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ARTICLE

Selective approach to thioesters and thioethers via sp^3 C-H activation of methylarenes

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Novel C-S cross-dehydrogenative coupling (CDC) approaches for selective synthesis of thioesters and thioethers has been developed via sp^3 C-H activation of methylarenes and subsequent functionalization. The reaction of methylarenes with thiols resulted in thioesters in the presence of $FeBr_2$/TBHP system, while treatment of methylarenes with thiols in the $Pd(OAc)_2/O_2$/TBHP system led to the formation of thioethers. Both the two green protocols demonstrate good functional group tolerance and satisfactory yields.

Introduction

The direct C−H activation path is now being extensively investigated as the short step and greener alternative to the traditional transition-metal-catalyzed couplings.[1] One such strategy, cross-dehydrogenative coupling (CDC) is of immense importance because it does not require substrate prefunctionalisation and enjoys the advantage of atom economy.[2] Screening of reference revealed that the CDC based protocols in the construction of a C–C[3], C-O[4], C-N[5] bond have been well achieved using transition metal catalysts in combination with various oxidants. However there is still a dearth of information on C-S bond formation. [6] In this regard, C-S bond formation and eventual synthesis of thioesters and thioethers involving C-H bond activation of methylarenes remains the cherished target.

Sulfur-containing compounds, especially thioesters and thioethers represent a class of important synthetic intermediates due to their ease of transformation.[7] Besides that, they are excellent building blocks for chemical biology, and hence are frequently found in a number of biologically active and medicinal agents.[8] Traditionally, thioethers were formed by coupling reactions between halides and thiols (or sulfur surrogates),[9] the SNAr reactions,[10] substitution reactions[11] etc. whereas thioesters were commonly prepared via acylation with thiols (or sulfur surrogates) and carboxylic acids [12], carboxylic acid halides [13], carboxylic acid anhydrides[14] or aldehydes[15]. Although, many elegant protocols for synthesis of thioethers and thioesters emerged, in accordance with the importance of them, the synthesis of thioethers or thioesters by unconventional approaches was always appreciable, particularly through functionalization of inert C−H bonds.

Methylarenes, derived from oil industry, constitute the most inexpensive and readily available feed stocks for chemistry. Of late, the sp^3 C−H activation and subsequent oxidative functionalization of methylarenes has drawn scientist's attention.[2e,16] Through this strategy, methyl arenes especially methylbenzenes are found to be useful precursors and have been used as $ArCOO-$,[17] $ArCO-$,[3h,5b,18] $ArCH_2O-$[19] and $ArCH_2-$ surrogates.[20] Considering the availability and economy of methylarenes and the few reported C-S formation examples via CDC protocol,[6a,21] herein we wish to report two novel methods for synthesis of thioesters and thioethers via sp^3 C-H activation of methylarenes, thus the use of more traditional coupling partners that require prefunctionalisation, including aryl halide, acyl halide, aryl acid, aryl aldehyde etc. are avoided.

Results and discussion

Encouraged by recent Fe-catalyzed synthesis of thioesters from thiols and aldehydes[15k], we initiate our work using toluene and 4-chlorobenzenethiol under the similar conditions (Fe, TBHP system). The aimed thioesters was observed in low yield by GC-MS along with the formation of benzaldehyde and disulfide[22] (Table 1, entry 7). In the process to optimize the reaction conditions, it was found that small amount of thioether was formed when $Pd(OAc)_2$ was used (Table 1, entry 6). Promising to selectively obtain thioesters and thioethers we optimized both the two reactions respectively.

As the reaction was conducted in water, surfactants may accelerate the reaction process. Screening nonionic and ionic surfactants revealed that nonionic surfactants such as Trion-X 100, Prij were ineffective, whereas in the presence of TBAI, the yield increased to 25%. The addition of 2%wt.SDS/water boosted the yield to 65% (Table 1, entries 7-10). Next, we examined the metal catalysts in a quest to improve the yield (Table 1 entries 3-6).

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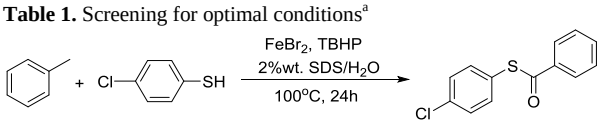
Table 1. Screening for optimal conditions[a]



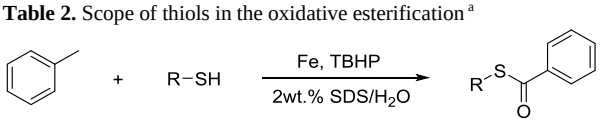
Entry	Change from the "standard conditions"	Yield[b]
1	none	65(80[c])
2	No $FeBr_2$	<1
3	$FeCl_2$ instead of $FeBr_2$	62
4	$Fe(acac)_3$ instead of $FeBr_2$	43
5	$Cu(OAc)_2$ instead of $FeBr_2$, no surfactant	8
6	$Pd(OAc)_2$ instead of $FeBr_2$, no surfactant	<1 (7[d])
7	No surfactant	12(80[e])
8	2 wt.% Prij L23 instead of 2 wt.% SDS	10
9	2 wt.% Trion X100 instead of 2 wt.% SDS	11
10	0.1eq TBAI instead of 2 wt.% SDS	25 (69[e])
11	BPO instead of TBHP	0 (95[e])
12	DTBP instead of TBHP	0 (10[e])

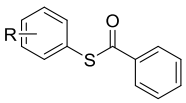
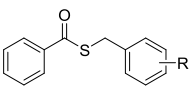
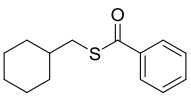
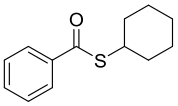
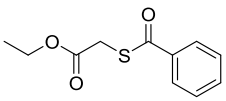
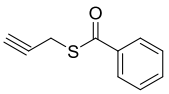
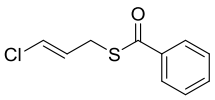
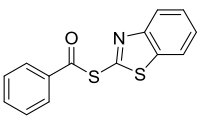
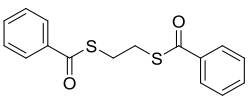
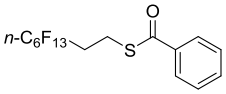
[a] Standard conditions: toluene 1.5 mmol, 4-chlorobenzenethiol 0.5 mmol, $FeBr_2$ 0.01 mmol, TBHP(70% in water) 1.5 mmol, 2% wt.SDS/H_2O 1 mL, 100 °C, 24 h. [b] the yield was determined by GC; [c] thiol was added in a dropwise fashion. [d] the yield of thioether. [e] the yield of disulfide.

Among all the catalysts tested, $FeBr_2$ was still found to be the best choice. Oxidants were also checked. In the presence of BPO, 4-chlorobenzenethiol converted to the corresponding disulfide quickly without the desired thioester formed (Table 1, entry 11), while in case of DTBP, most starting materials were not converted (Table 1, entry 12). Among all the conditions, the formation of disulfide seemed inevitable. When the thiol was added in a dropwise fashion, the yield of thioester could increase to 80% (Table 1, entry 1).

Having established the optimized reaction conditions, the present oxidative esterification reactions were then implemented on the reaction between toluene and a series of substituted thiophenols and thiols. As is shown in Table 2, thiophenols containing electron-donating or electron-withdrawing groups reacted smoothly with toluene, giving thioesters in moderate to good yields (Table 2, **3a**-**3e**). There is a decrease of yield when thiophenols bear methyl group at different positions (Table 2, **3b**, **3c**). It was found that the methyl group can also be activated with small amount of mercaptobenzaldehyde and mercapto thioesters observed. Alkyl thiols can also successfully couple with toluene (Table 2, **3f**-**3k**, **3m**, **3o**). In general, the product yields for the alkyl thiols are lower than those of thiophenols. Especially, sterically demanding substrates yield the product in a lower level (Table 2, **3j**). It is worth to note that thiols bearing fluorous tail can also undergo this coupling which may be useful in fluorine chemistry[23] (Table 2, **3p**). We further checked heterocyclic thiophenols. To our delight, the reaction between toluene and benzo[d]thiazole-2-thiol afforded the aimed product (Table 2, **3n**) in moderate yield. Unfortunately, the reaction failed to proceed in the case of 1H-benzo[d]imidazole-2-thiol witha collection of byproducts including open ring product, C-N coupling product instead of the aimed thiester obtained (Table 2, **3q**).

Table 2. Scope of thiols in the oxidative esterification [a]



Entry	Product			Yield(%)[b]
1		R=4-Cl	**3a**	82
2		R=2-CH_3	**3b**	45
3		R=4-CH_3	**3c**	56
4		R=4-F	**3d**	66
5		R=4OCH_3	**3e**	84
6		R=4-F	**3f**	64
7		R=H	**3g**	71
8		R=4-CH_3	**3h**	72
9			**3i**	65
10			**3j**	10
11			**3k**	35
12			**3l**	0
13			**3m**	52
14			**3n**	46
15			**3o**	42[c]
16			**3p**	45

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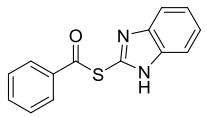
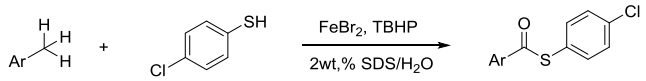
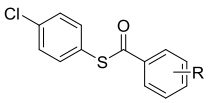
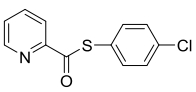
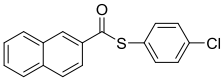
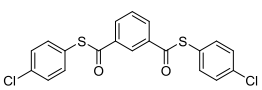
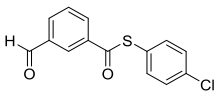
17		**3q**	0

[a] Reaction conditions: toluene 1.5 mmol, thiol 0.5 mmol, $FeBr_2$ 0.01 mmol, TBHP(70% in water) 1.5 mmol, 2 wt.%SDS/H_2O 1 mL, 100 °C, 24 h;[b] Isolated yield; [c] Reaction conditions: toluene 1.5 mmol, thiol 0.25 mmol, $FeBr_2$ 0.02 mmol, TBHP(70% in water) 3 mmol, 2 wt.% SDS/H_2O 1 mL, 100 °C, 36 h.

After that we turned our attention to the functional group compatibility of methylarenes. Methylarenes containing a methyl-, chloro-, bromo- or methoxy-substituent were all tolerated under the reaction conditions (Table 3, **4a**-**4d**, **4f**-**4g**). However, methylarene bearing a $–N(CH_3)_2$ substituent failed to couple with the thiophenol. The demethylation of the N-CH_3 was observed under the standard condition.The steric hindrance had little influence with similar yields obtained with **4b**, **4g**. When there are more than one methyl group in the benzene ring (for example **4k**), the "dithioester" could be afforded when added more TBHP and extended the reaction time. Acompany with **4k**, S-(p-tolyl) 3-formylbenzothioate **4k'** was also observed. Remarkably, naphthalene-containing methylarenes could also serve as coupling partners with thiols (Table 3, **4j**). But unfortunately, only trace amount of the aimed product was observed when pyridine-containing substrate was used.

Table 3. Scope of methylarenes in the oxidative esterification [a]

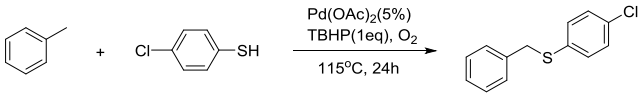


Entry	Product		Yield(%) [b]
1		R=4-CH_3 **4a**	69
2		R=2,4-Cl **4b**	79
3		R=3-Br **4c**	77
4		R=4-OCH_3 **4d**	83
5		R=4-$N(CH_3)_2$ **4e**	Trace
6		R=4-NO_2 **4f**	52
7		R=4-Cl **4g**	80
8		R=4-CF_3 **4h**	Trace
9		**4i**	Trace
10		**4j**	75
11[c]		**4k**	45
		**4k'**	15

[a] Reaction conditions: toluene 1.5 mmol, thiol 0.5 mmol, $FeBr_2$ 0.01 mmol, TBHP(70% in water) 1.5 mmol, 2 wt.% SDS/H_2O 1 mL, 100 °C, 24 h. [b] Isolated yield. [c] Reaction conditions: toluene 1.5 mmol, thiol 1 mmol, $FeBr_2$ 0.02 mmol, TBHP(70% in water) 3 mmol, 2 wt. % SDS/H_2O 1 mL, 100 °C, 36 h.

As mentioned above, thioether instead of thioester was obtained when $FeBr_2$ was replaced by $Pd(OAc)_2$. Aimed to selective preparation of thioethers, we further explored the palladium-catalyzed CDC thiolation. Details of optimizations are shown in Table 4. The yield of the desired thioether slightly increased when the reaction was moved from the Argon atmosphere to the open air albeit in a low yield (Table 4, entry 9). It indicated that oxidants may play a key role in the CDC process, thus we put the reaction in a pure oxygen atmosphere (Table 4, entry 1) and increased the equivalent of TBHP respectively (Table 4, entry 11). The addition of excess TBHP had no positive effect to the present reaction but produced more benzaldehyde and sulfur oxidation products in adverse. Gratefully, when the reaction was conducted under oxygen atmosphere, the yield increased to 86%. In view of this result, TBHP may not be necessary. However, the yield dropped sharply in absence of TBHP (Table 4, entry 7). It is known that thioether may be oxidised by TBHP under heated conditions, however, only trace amount of sulfur oxidation products were observed with the present conditions . As same with the above reaction, surfactant was also tried to accelerate the reaction, but it didn't give any improvement(Table 4, entry 6). Finally, some commercial available palladium catalysts and copper catalysts were examined. Still, $Pd(OAc)_2$ was the best choice (Table 4, entries 3-5). And a decrease in catalyst loading (5 mol %) had an adverse effect on product yield (Table 4, entry 12).

Table 4. Optimal conditions for palladium-catalyzed CDC thiolation [a]



Entry	Change from the "standard conditions"	Yield[b]
1	none	86
2	No $Pd(OAc)_2$	0
3	$Cu(OAc)_2$ instead of $Pd(OAc)_2$	0
4	$Pd(PPh_3)_2Cl_2$ instead of $Pd(OAc)_2$	55
5	$Pd(dppf)Cl_2$ instead of $Pd(OAc)_2$	37
6	The addition of SDS (0.02 eq) as a surfactant	84
7	No TBHP, 48h	16
8	Under Ar atomosphere	8(12[c])
9	In the air	30

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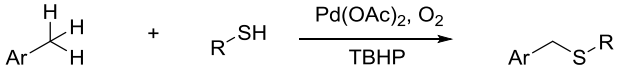
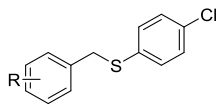
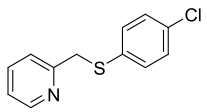
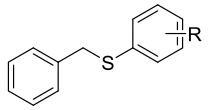
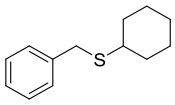
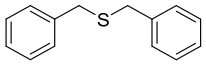
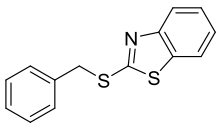
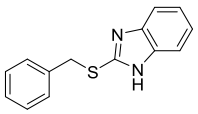
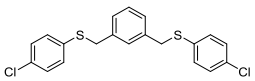
10	the addition of $FeBr_2$	26(35[d])
11	3eq TBHP	21(55[c], 9[d])
12	$Pd(OAc)_2$ loading decreased to 5%	62

[a] Standard conditions: toluene 1.5mmol, 4-chlorobenzenethiol 0.5mmol, $Pd(OAc)_2$ 0.05mmol, TBHP(70% in water) 0.5mmol, 1 atom O_2, 115°C, 24h. [b] The yield was determined by GC. [c] The yield of benzaldehyde. [d] The yield of thioester.

Then these optimized conditions were applied for the reaction of structurally different methylarenes and thiophenols or thiols. A series of unsymmetrical aryl alkyl thioethers could be successfully prepared from substituted methylarenes whereby electronic effect showed no significant association with the yield (Table 4, **5a**-**5g**). Differently with the thioesterification described above, the steric hindrance affected the product yield significantly(Table 4, **5b** ,**5g**). Like the above esterification reaction, the "di-thioether" could be obtained under harsher reaction conditions (Table 5, **5q**). We have also investigated the applicability of our method using different thiols or thiophenols. As expected, thiophenols could easily convert to the aimed products for all the electronic-donating and the electronic-withdrawing substituents (Table 5, **5i**-**5l**). Alkyl thiols including benzyl thiol and cyclohexanethiol were also applied for the coupling. Symmetric thioether was obtained in good yield with benzyl thiol (Table 5, **5n**), while cyclohexanethiol reacted sluggishly and a 55% yield was obtained by prolonging the reaction time (Table 5, **5m**). At last, heterocyclic thiols were tested. Similarly, benzo[d]thiazole-2-thiol underwent the present reaction smoothly while benzo[d]imidazole-2-thiol failed this reaction (Table 5, **5o**, **5p**).

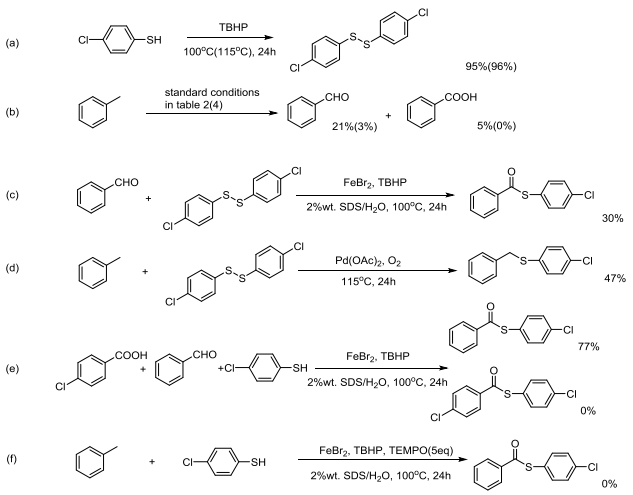
Table 5. Scope of methylarenes in the oxidative thioetherification [a]



Entry	Product			Yield(%)[b]
1		R=-H	**5a**	84
2		R=4-F	**5b**	77
3		R=4-CH_3	**5c**	62(4[c])
4		R=4-NO_2	**5d**	58
5		R=4-CN	**5e**	62
6		R=4-Br	**5f**	83
7		R=2-F	**5g**	71
8			**5h**	8
9		R=2-CH_3	**5i**	72
10		R=4-CH_3	**5j**	77
11		R=4-OCH_3	**5k**	70
12		R=4-F	**5l**	46
13			**5m**	55[d]
14			**5n**	80
15			**5o**	80
16			**5p**	0
17			**5q**	28[e]

[a] Reaction conditions: methylarenes 1.5mmol, thiol or thiophenol 0.5mmol, $Pd(OAc)_2$ 0.05mmol, TBHP(70% in water) 0.5mmol, 1atm O_2, 115°C, 24h. [b] isolated yield. [c] the yield of 1,4-bis(((4-chlorophenyl)thio)methyl)benzene. [d] reaction time 48h. [e] reaction conditions: m-xylene 1.5mmol, thiophenol 1mmol, $Pd(OAc)_2$ 0.1mmol, TBHP(70% in water) 1mmol, 1atm O_2, 120°C, 36h.

To gain insight into the catalytic pathway of the two reactions, we conducted some mechanistic experiments (Scheme 1). In the presence of TBHP, thiophenol could easily convert to the disulfide.



Scheme 1. Controlled experiments for preliminary mechanistic studies.

Thus disulfide was used for the developed two reactions to replace the thiophenol. Under the standard conditions, both thioesterification and thioetherification could proceed, but with lower yields. It means thiophenol was more appropriate for the two reactions although the formation disulfide was inevitable. During the reaction of toluene with $FeBr_2$/TBHP, both aldehyde and benzoic acid were observed while in the $Pd(OAc)_2/O_2$ conditions, only trace amount of aldehyde was observed. So we further put benzaldehyde and 4-chlorobenzoic acid simultaneously into the thioesterification reaction. The

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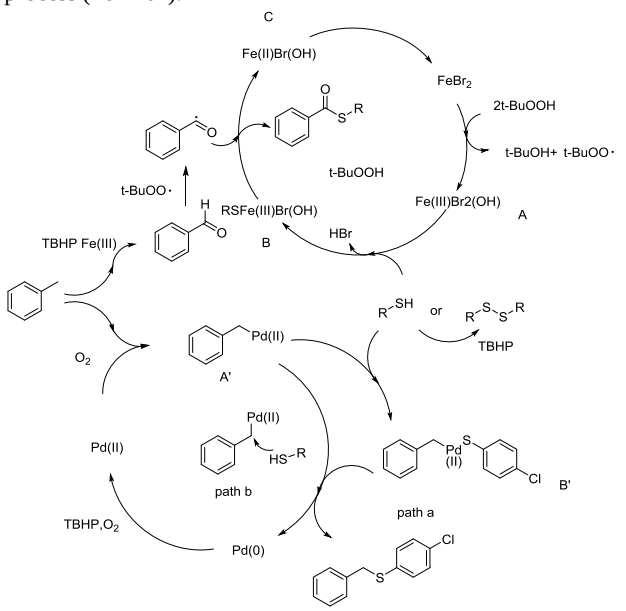
crossover experiment showed that benzaldehyde reacted with 4-chlorobenzenethiolunder the present experimental conditions which ruled out the usual esterification of acid and thiol. Also, the thioesterification reaction was treated with a radical inhibtor. When excess TEMPO (5 equivalents) was added, no thioester could be observed which indicated that the Iron-catalyzed thoesterification may follow a radical mechanism.

Based on the above results and in combination with the already known mechanism in the literature15j, a plausible mechanism was proposed as shown in scheme 2. In the Iron-catalyzed reaction, toluene was firstly oxidized to form benzaldehyde which further reacted with t-BuOO• to give an acyl radical. On the other hand, iron salts promoted TBHP to form t-BuOO• and the $FeBr_2$ converted to immediate A which further reacts with the thiol or disulfide to give an iron(III) thiolate complex B and release HBr. Then the complex B traps the acyl radical to provide the aimed thioester and complex C, C reacted with HBr to regenerate $FeBr_2$ to close the circle.

As for the Pd-catalyzed cycle, the catalytic cycle starts with Pd^{II}-mediated C-H cleavage to form benzyl Pd complex **A'**. The benzylation products may result from nucleophilic attack on the benzylic carbon by thiophenol (Path A). Alternatively, undergo ligand exchange to afford benzyl Pd(II)carboxylate **B'**, and subsequent reductive elimination yields thioether products (Path B). The Pd^0 species generated in Path **A** or **B** is oxidised to Pd^{II} by O_2 to continue the catalytic cycle. It should be noted that the existing TBHP may accelerate the C-H cleavage and palladium oxidation process (Pd^0-Pd^{II}).



Scheme 2. Proposed mechanism for the Fe-catalyzed thioesterification and Pd-catalyzed thioetherification via sp^3 C-H activation of methylarenes.

Experimental Section

Melting points are uncorrected. All commercial materials were used without further purification. Thiols were synthesized according to the literature [24]; TBHP used was 70% TBHP in water. GC-MS analyses were performed on an Agilent 7890A-5975C instrument (Column: DB-5 MS). NMR was recorded on Bruker DRX 500 and tetramethylsilane (TMS) was used as a reference. Elemental analysis was performed on a Yanagimoto MT3CHN recorder. Preparative high performance liquid chromatography was performed on an Agilent Technologies 1200 Column: XDB- C18 9.6×250mm.

General procedure for synthesis of thioesters

A 5 ml vial with condenser was charged with toluene (1.5 mmol), $FeBr_2$ (0.01mmol), TBHP(1.5 mmol), 2% wt. SDS /H_2O (2 ml), thiol (or thiophenol)(0.5mmol) was then added in a dropwise (in portion for solids) at 100°C. The reaction mixture was stirred at 100 °C for 24h. Upon completion, the reaction mixture was then cooled, extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. After filtration, the organic solutions were concentrated and the residue was purified by column chromatography on silica gel to give the pure product (hexane/ethyl acetate=20/1).

General procedure for synthesis of thioethers

A mixture of toluene (1.5 mmol), $Pd(OAc)_2$ (0.05 mmol), TBHP(1.5 mmol) thiol (thiophenol)(0.5mmol) was introduced in a pressure reactor. The suspension was stirred at 115 °C for 24 h under 1 atm of oxygen. After this, the pressure was released and the mixture was extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. After filtration, the organic solutions were concentrated and the residue was purified by column chromatography on silica gel to give the pure product (hexane/ethyl acetate=50/1).

Conclusions

In summary, we developed two facile and efficient protocols thus thioesters and thioethers can be selectively prepared via the Fe-catalyzed C-H functionalization thioesterification and Pd-catalyzed C-H functionalization thioetherification respectively. The major advantages of this method include the use of toluene as the benzylation or benzoylation reagent and oxygen or TBHP as the green oxidant, which owns high atom economy, avoids the prefunctionalization of substrates and reduces the production of chemical wastes. In addition, the two rarely reported protocols demonstrate good functional group tolerance and moderated to good yields.

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Notes and references

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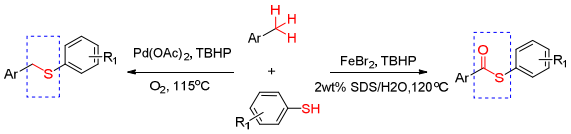
Graphic abstract



Text

Novel CDC approaches for synthesis of thioesters and thioethers was developed via sp^3 C-H activation of methylarenes and subsequent functionalization