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Direct oxidative coupling of thiols and benzylic ethers *via* C(sp^3)-H activation and C-O cleavage to lead thioesters

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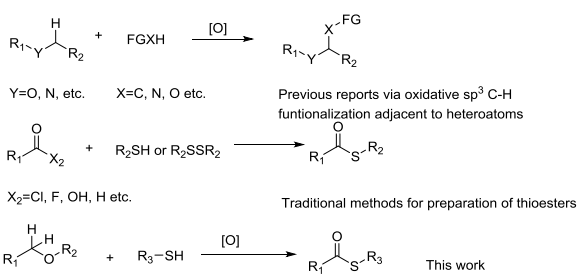
An unprecedented C-S formation method *via* the direct oxidative C(sp^3)−H bond functionalization and C-O cleavage of benzylic ethers was developed. Various thioesters including thioester structure containing drug intermediate could be achieved via this convenient, metal and base free method in satisfactory yields.

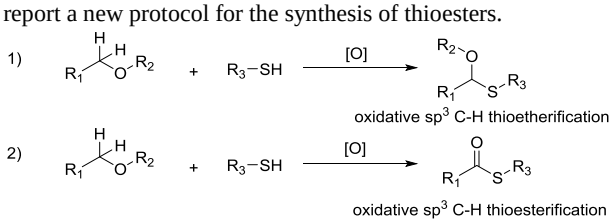
The functionalization of C−H bonds is being extensively investigated in recent years because of its atom-economic and environmental sustainability.[1] Particularly, the direct oxidative functionalization of inert C(sp^3)−H bonds has received much attention.[2] The prodigious achievements in this area mainly include C(sp^3)–H bond functionalization of cycloalkanes or benzylic arenes,[3] C(sp^3)–H bond functionalization with the assistance of a chelating group,[4] and the functionalization of C(sp^3)–H bond adjacent to heteroatoms.[5] The last strategy, C(sp^3)–H bond activation adjacent to heteroatoms especially draw our attention due to the molecular diversity of the substrates, and no requirement of a directing group. Up to date, the C-C, C-N and C-O formation via this strategy have been well documented,[6] however the C-S bond formation utilizing this strategy has fewly reported (Scheme 1).



Scheme 1. Approach for the C-S bond foramtion via C (sp^3)-H activation

Sulfur-containing compounds, especially thioesters represent a class of important synthetic intermediates and have momentous biological and pharmaceutical values,[7] and hence are frequently found in a number of biologically active and medicinal agents.[8] Typically, thioesters were prepared *via* acylation of thiols (or the sulfur surrogates) with carboxylic acids[9], carboxylic acid halides[10], carboxylic acid anhydrides[11] or aldehydes[12]. In recent years, many other elegant protocols, especially the C-H activation paths, for synthesis of thioesters have also emerged.[13] Although a great number of thioester synthesis protocols have existed, in accordance with the importance of thioesters, the synthesis of thioesters by unconventional approaches was always appreciable, particularly through functionalization of inert C−H bonds.

As a starting point, we planned to explore the oxidative sp^3 C-H thioetherification with benzylic ethers and thiols (Scheme 2, eq.1). In the course of this study, an unexpected thioester product was obtained in the presence of excess oxidants (Scheme 2, eq.2). No literature, however, has reported the synthesis of thioesters via the oxidative coupling of benzylic ethers with thiols. Here, we wish to report a new protocol for the synthesis of thioesters.

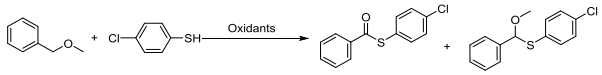


Scheme 2. The C-S bond formation via oxidative C(sp^3)-H functionalization

We initiated our work using benzyl methyl ether and 4-chlorobenzenethiol as substrates to optimized the reaction conditions. As is shown from Table 1, accompany with the desired thioester product **3a**, the byproduct thioether **3a'** was also observed. The oxidant is crucial for both the conversion of benzyl methyl ether and the selectivity betwwen **3a** and **3a'**. Among all the oxidants checked, di-tert-butylperoxide (DTBP) was the best choice (Table 1, entries 4-7). The coupling between benzyl methyl ether and 4-chlorobenzenethiol afforded thioether **3a'** as major product in the

presence of DTBP (1.5 equivalents) (Table 1, entry 2). Increasing the amount of DTBP to 3 equivalents, a 85% yield of **3a** was obtained (Table 1, entry 7 *vs* entry 2). When more DTBP (4 equiv.) was added, the yield didn't show any significant improvement (Table 1, entry 8). The reaction temperature was also screened, 120 ^{o}C was the most appropriate temperature (Table 1, entries 2, 10-12)., relatively lower yields were obtained at a higher temperature which may due to the formation of methyl benzoate

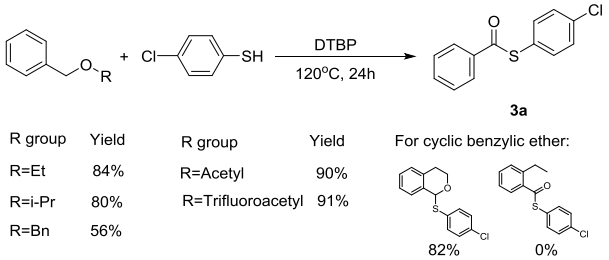
Table 1. Screening for optimized conditions[a]



Entry	Oxidants	Time/h	Temp/ ^{o}C	Yield of **3a** %[b]	Yield of **3a'** %[b]
1	-	24	120	0	0
2	DTBP (1.5 eq)	6	120	3	81
3	DTBP (2 eq)	24	120	54	30
4	TBHP (3 eq)	24	120	0	10
5	BPO (3 eq)	24	120	0	0
6	DDQ (3 eq)	24	120	1	26
7	DTBP (3 eq)	24	120	85	0
8	DTBP (4 eq)	24	120	85	0
9	DTBP (3 eq)	36	120	87	0
10	DTBP (3 eq)	24	100	7	38
11	DTBP (3 eq)	24	130	68	0
12	DTBP (3 eq)	24	140	57 (22[c])	0

[a] Reaction conditions: 4-chlorobenzenethiol 1.5mmol, benzyl methyl ether 1mmol. [b] HPLC yield. [c]The yield of methyl benzoate

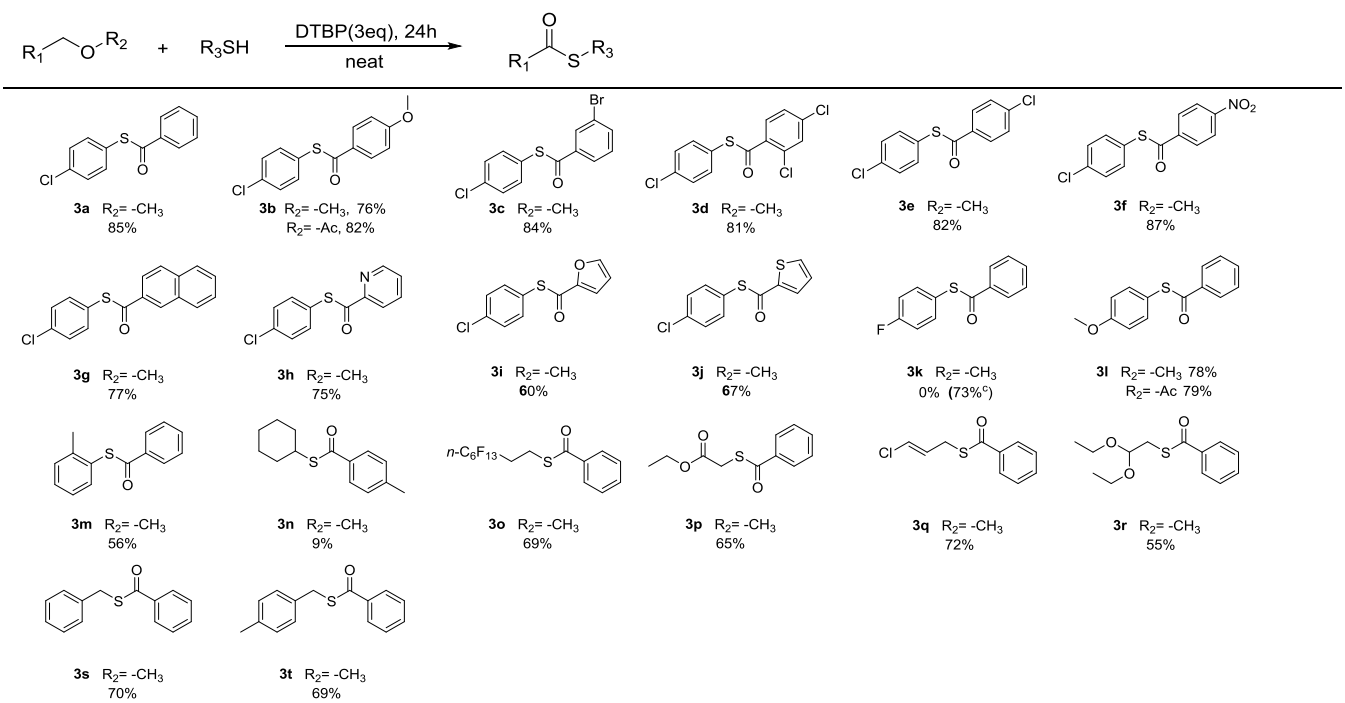
With the optimized conditions in hand, we firstly checked the substrate scope of benzylic ethers. Besides benzyl methyl ether and symmetric benzyl ether, a series of asymmetric benzylic ethers or benzylic esters were all tolerated the reaction conditions (Scheme 3). Comparatively, benyzlic esters such as benzyl acetate and benzyl 2,2,2-trifluoroacetate coupled with 4-chlorobenzenethiol more efficiently. Cyclic benzylic ether such as isochroman was also checked. Unlike the linenear ethers, only 1-((4chlorophenyl) thio)isochromane was formed in the yield of 82%.



Scheme 3. The oxidative thioesterification of a series of benzylic ethers or esters.

The synthetic merit of this protocol was then illustrated by varying the substrates, and the results are summarized in Table 2. A wide range of substituted benzyl methyl ethers were found to be compatible with this transformation (Table 2, **3b**-**3g**). In particular, 2,4-dichloro-benzyl methyl ether and 4-chloro-benzyl methyl ether smoothly coupled with thiophenol to deliver thioesters in comparable yields (Table 2, **3d**, **3e**), indicating that the steric effects have little influence on the yield.

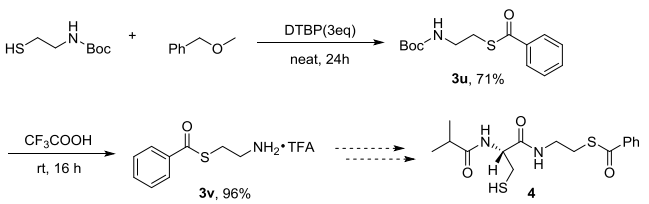
Table 2. Substrate scopes of the oxidative C(sp^3)–H thioesterification [a],[b]



[a] Reaction conditions: thiols 1.5mmol, ether 1mmol, DTBP 3mmol, 120^{o}C, 24h. [b] Isolated yield. [c] The yield of (phenylmethylene)bis((4-fluorophenyl)sulfane).

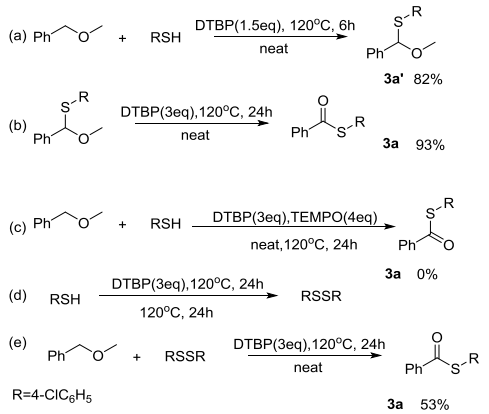
Besides benzylic ethers, heterocyclic-containing ethers including 2-(methoxymethyl)pyridine, 2-(methoxymethyl)furan and 2-(methoxymethyl)thiophene were also tolerated under the optimized reaction conditions (Table 2, **3h-3j**). A series of thiophenols were then evaluated. Thiophenols, including the steric demanding 2-methylbenzenethiol (with lower yields than others), turned out to be effective substrates for this reaction (Table 2, **3l-3m**). When 4-fluorobenzenethiol was subjected to the optimized conditions, a *di*-substituted product, (phenylmethylene)bis((4-fluorophenyl)sulfane), was obtained (Table 2, **3k**). To our delight, the thioesters could also be achieved in the presence of alkyl thiols (except for the steric demanding cyclohexanethiol **3n**), which furnished the corresponding products in moderate to good yields (Table 2, **3q-3u**). Notably the oxidative thioesterification of fluorous thiols could also be achieved which may be useful in fluorine chemistry (Table 2, **3p**).[14]

To further highlight the potential advantage of the methodology, thioester **3v**, a crucial intermediate en route to drug molecules which displays potent anti-HIV properties in human macrophages, was synthesized by the oxidative thioesterification of benzyl methyl ether. Compared to the previous reports using benzoyl chloride, this method is easy to handle and avoids the usage of organic solvent which may have potential values on commercial run. [15]



Scheme 4. A potential application of the protocol in organic synthesis

To gain insight into the mechanism of this reaction, we then conducted some controlled experiments. As mentioned above, the coupling of benzyl methyl ether with 4-chlorobenzenethiol afforded byproduct **3a'** in good yields. When **3a'** was further stirred in the presence of excess DTBP, it could convert to **3a**. To further demonstrate whether **3a'** was the intermediate of the present protocol, the reaction process were tracked by variation with time (Fig 1). As expected, the C-S coupling occurred to form the corresponding thioethers **3a'**. Then thioether **3a'** converted to thioesters **3a** by sequence. It can also conclude that benzyl methyl ether showed higher reactivity than thioether **3a'** with only trace amount of **3a** obtained in the former 6 hours. After that excess TEMPO was added as a radical inhibitor. As expected, no desired product was observed, indicating that the present reaction may follow a radical mechanism. Also the disulfide was formed along the reaction process. We further checked whether the disulfide could participate in the reaction. The disulfide could couple with benzyl methyl ether to afford the thioester, but comparatively, the yield was lower.



Scheme 5. Controlled experiments for the oxidative thioesterification

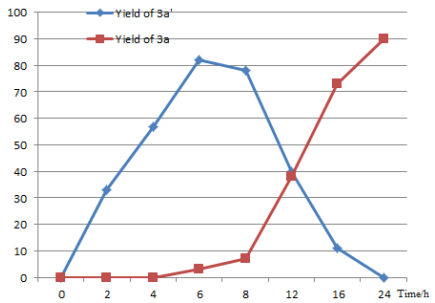
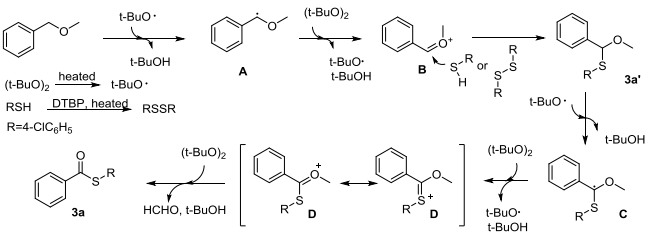


Fig1. Tracking of the coupling by variation with time

Based on the experiment results and the reported literatures [2d], a plausible reaction mechanism was proposed in Scheme 3. DTBP decomposed into the *tert*-butoxyl radical at first under heating. A hydrogen abstraction of the C–H bond adjacent to an oxygen atom produced radical intermediate **A** which was further oxidized to intermediate **B**. The thiols or disulfide coupled with **B** to give **3a'**. After that, the second dehydrogenation process occurred to form intermediate **C**, which was further oxidized to give the final thioester products in the presence of excess oxidants.



Scheme 6. Proposed mechanism.

Conclusions

In summary, an unprecedented protocol for the synthesis of thioesters *via* the direct oxidative cross-couplings of benzylic ethers with thiophenols or thiols in metal-free conditions has been developed. This method was convenient and easy-to-handle with the use of DTBP as the only green oxidant. In addition, the method was applicable for a wide substrate

scopes and provided alternative routes for preparation of potential pharmacological activity-containing thioester derivatives.

Notes and references

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Electronic Supplementary Information (ESI) available: [spectral data for all reported compounds]. See DOI: 10.1039/c000000x/

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