Late-stage C–H thiolation via sulfonium salts using β -sulfinylesters as the versatile sulfur source

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Article

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Abstract

Organic sulfides form the core scaffold of a wide range of pharmaceuticals, natural products, and materials, and serve as key intermediates in synthesis. Prior methods to organic sulfides require the use of transition metal (TM) catalysts, prefunctionalized or chelating group-containing substrates, and elevated reaction temperatures. A general TM-free C–H thiolation protocol using readily accessible sulfur source is highly desirable. Herein, we disclose a direct C(sp)–, C(sp²)–, and C(sp³)–H thiolation reaction using β -sulfinylesters as the versatile sulfur source. The key step of this protocol is chemoselective C–S bond cleavage of the sulfonium salts that is in situ formed from the corresponding (hetero)arenes, alkenes, alkynes, and 1,3-dicarboxyl compounds with β -sulfinylesters. The successful capture of acrylate byproduct supports a retro-Michael reaction mechanism. This method is expected to be used widely because of several advantageous aspects including TM-free, mild reaction conditions, and broad substrate scope including drug molecules.

Introduction

Organic sulfides have been widely found as privileged structures in pharmaceuticals,¹ natural products,² and materials.³ They are also valuable precursors to sulfones- and sulfoxides-containing drugs that exhibit significant biological activities.⁴ The most convergent approaches to these compounds are the transition metal (TM)-catalyzed C–S cross-coupling reactions of aryl/vinyl (pseudo)halogen with thiols/disulfides^{5–8} and the TM-catalyzed directing-group assistant C–H bond thiolations of arenes.^{9,10} The requirement of prefunctionalized or chelating group-containing substrates, TM catalysts, and elevated reaction temperatures sharply limited their applications. Alternatively, the direct C–H thiolation of highly electron-rich aromatics using electrophilic thiolation reagents could proceed under TM-free conditions, which limited to deliver aryl sulfides.¹¹

Recently, sulfonium salts have emerged as powerful intermediates for the site-selective late-stage C–H functionalization of arenes,¹² in which sulfides, such as tetrahydrothiophene, thianthrene, and dibenzothiophene were formed quantitatively as byproducts (Scheme 1a).^{13–35} In addition, the selective cleavage of one of the three C–S bonds of aryl sulfonium salts *via* nucleophilic substitution were also realized to give aryl sulfides (Scheme 1b).^{36–44} While this strategy is promising, alkenyl, alkynyl, and alkyl sulfonium salts were not tolerated due to the fact that both of alkenyl and alkynyl sulfonium salts are good electrophilic Michael acceptors,^{45–49} and alkenyl C(sp²)–S, C(sp)–S, and C(sp³)–S bonds of sulfonium salts are more prone to be attacked by nucleophiles than aryl C(sp²)–S bond.^{36,50,51} Undoubtedly, the development of a general, practical, and TM-free C–H thiolation reaction for the construction of functionalized sulfides, including aryl, alkenyl, alkynyl, and alkyl sulfides, is highly desirable. We envisioned that the chemoselective C–S bond cleavage of β -sulfonium esters may occur *via* retro-Michael reaction, giving otherwise inaccessible sulfides. Herein, we reported the direct C–H thiolation reaction of (hetero)arenes, alkenes,^{52,53} alkynes,^{54–56} and 1,3-dicarboxyl compounds using β -sulfinylesters as easily accessible and versatile thiolation reagents (Scheme 1c). This one-pot two steps

process proceeds through site-selective C–H sulfonium salt formation followed by chemoselective C–S bond cleavage under TM-free conditions with broad functional group tolerance.

Results

Reaction development. Initially, we employed methyl 3-(*p*-tolylsulfinyl)propanoate **1a**, toluene **2a** as the model substrates to optimize the conditions of the TM-free C–H thiolation reaction. After extensive screening of various reaction parameters, the optimal conditions were achieved to be **1a** (1.3 equiv), **2a** (0.3 mmol), Tf₂O (1.3 equiv), solvent (3 mL) under nitrogen atmosphere at room temperature for 1 h, then Et₃N (5 equiv) at room temperature for 1 h (Table 1 entry 1). A series of bases were screened, and no better yields were obtained than Et₃N (Table 1 entries 2–5). Switching the solvent to CH₃CN only provide the desired product in low yield (Table S1, entry 6). The yield was reduced to 30% when TFAA was used in lieu of Tf₂O (entry 7). A similar result was obtained using ethyl ester **1b** as the thiolation reagent (entry 8). However, *tert*-butyl ester **1c** only delivered the desired product in 23% yield (entry 9).

With the established optimal reaction conditions in hand, we first investigated the substrate scope of arenes (Table 2). A wide range of substituted benzenes could be converted to the corresponding diaryl sulfides in good yields (**3a–s**). Functional groups including cyclopropyl, halogens, allyloxy, and ester were well tolerated in this transformation. It is noteworthy that the reactivity of this thiolation reaction was not affected by steric hindrance of the arene substrates (**3q** and **3s**). To our delight, heteroaromatics could also be applied to the reaction system without obstacle (**3t–w**). Among them, indole, pyrrole, and thiophene could give the corresponding products in the excellent yields. Although quinoline derivative was less reactive under standard conditions, increasing reaction temperature slightly improved product yield (**3u**). Notably, this strategy was successfully applied to the late-stage C–H thiolation of a variety of drug-like molecules (**3aa–af**). (S)-4-benzyl-2-oxazolidinone derivative, nimesulide, bifonazole, L-phenylalanine derivative, estrone derivative and D-salicin derivative all could be modified by this method. We then examined the reaction of 1,2-dimethoxybenzene **2o** with a range of β-sulfinylesters. Aryl sulfoxides bearing electron-donating groups or halogens had good reactivity (**4a–f**), whereas aryl sulfoxide with a nitro group only delivered the desired product in 26% yield (**4g**). In addition, pyridyl and thienyl sulfoxides were compatible, albeit the desired products were formed in low yields (**4h** and **4i**). Remarkably, alkyl sulfoxides including benzyl sulfoxide were applicable to the reaction system, giving the desired products in good yields (**4j–l**).³⁶

Inspired by these exciting results, we discussed the application of this strategy in the synthesis of more challenging alkenyl, alkynyl, and alkyl sulfides (Table 4). Styrenes containing electron-donating and -withdrawing groups all have good adaptability (**6a–j**). It is worth mentioning that high *E*-selectivities were obtained in all cases. Vinyl sulfide **6k** and allyl sulfide **6k'** were formed in 93% combined yield using α-methylstyrene as substrate. 1,1-Diphenylethene and triphenylethene were smoothly converted to the desired alkenyl sulfides in 89% and 46% yields, respectively (**6l** and **6m**). When tetraphenylethene was subjected to the reaction system, only aryl C–H thiolation product was observed (**6n**). It should be noted

that compounds (**6l–n**) were promising aggregation-induced emission luminogens.⁵³ Additionally, a range of aryl and alkyl sulfoxides could also donate the corresponding alkenyl sulfides without obstacle (**6o–y**).

Next, we proceed to investigate the application of this strategy to C(sp)–H thiolation. Gratifyingly, the reaction was proved to be applicable to C(sp)–H thiolation of aryl alkynes (**8a–h**). Low reactivity of alkyl alkynes was observed, and only 17% yield was obtained (**8i**). In addition to thioarylation (**8j–p**), thioalkylation of C(sp)–H bond was also successful (**8q** and **8r**).

Finally, we found that 1,3-dicarbonyl compounds could be thiolated with β -sulfinylesters to give a variety of alkyl sulfides in 38–88% yields (**10a–i**).

We have carried out a gram-scale reaction of dimethyl 3,3'-sulfinyldipropionate **1m** and *p*-xylene **5m**, giving the sulfide **11** in 74% yield (Fig. 2a). We then sought to investigate the possibility of performing iterative C–H thiolation, wherein the newly synthesized sulfoxide **12** may serve as the starting material for an additional C–H thiolation. Delightfully, sulfides **13** and **14** were formed in 72% and 73% yields from 4-bromostyrene **5i** and D-salicin derivative **2af**, respectively (Fig. 2b). Finally, the proposed methyl acrylate byproduct could be captured via Heck reaction to give **15** and **16** in 25% and 40% yields, respectively (Fig. 2c).

Discussion

In summary, we have developed a general and practical C–H thiolation of (hetero)arenes, alkenes, alkynes, and 1,3-dicarbonyl compounds using β -sulfinylesters as sulfur source that requires no preactivation of the substrates. This TM-free protocol proceeds via site-selective C–H sulfonium salt formation followed by retro-Michael reaction to give a vast number of organic sulfides with broad functional group tolerance. The synthetic importance of this method was demonstrated by late-stage C–H functionalization of drug molecules, and iterative C–H thiolation. We believed that this method should have broad applications in the future.

Methods

Preparation of 3a. A dried 15 ml Schlenk tube was charged with methyl 3-(*p*-tolylsulfinyl)propanoate **1a** (88.3 mg, 0.39 mmol, 1.3 equiv), toluene **2a** (27.6 mg, 0.3 mmol, 1.0 equiv), and DCM (3 mL). Tf₂O anhydride (110.0 mg, 0.39 mmol, 1.3 equiv) was added at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 1 h. Upon completion, Et₃N (0.2 mL, 5.0 equiv) was added and the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated under vacuum, and purified by preparative thin layer chromatography (PTLC) with hexane to give the corresponding product **3a** (59.2 mg, 92%).

Declarations

Data availability

All relevant data are available in Supplementary Information and from the authors.

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Author contributions

Y.C. developed the C–H thiolation reaction. S.W., Q.T., and Y.Z. explored the substrate scope. G.C. conceived and supervised the project. G.C. wrote the manuscript.

Competing interests

The authors declare no competing interests.

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Tables

Due to technical limitations the Tables are available as a download in the supplementary files.

Figures

Figure 1

Chemoselective C–S bond cleavage of the sulfonium salts. (a) TM-catalyzed C–S bond cleavage. (b) C–S Bond cleavage by nucleophiles. (c) C–S bond cleavage via retro-Michael reaction.

Figure 2

Gram-scale, iterative C–H thiolation, methyl acrylate capture reactions. a Gram-scale reaction. b Iterative C–H thiolation reaction. c Methyl acrylate capture reaction.

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