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Nucleophilic Functionalization of Thianthrenium Salts under Base Conditions

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Abstract

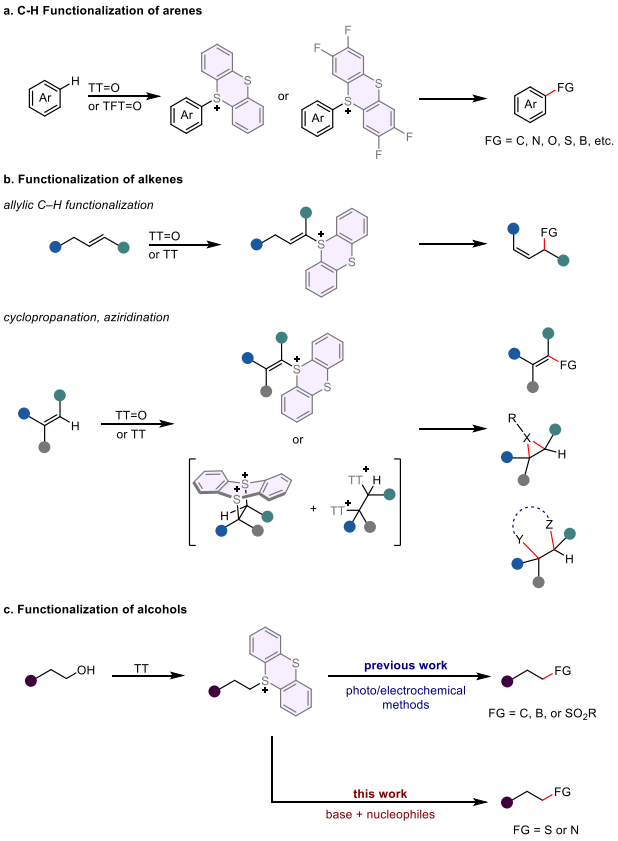
In recent years, S-(alkyl) thianthrenium salts have become an important means of functionalizing alcohol compounds. However, additional transition-metal catalysts and/or visible light are required. Herein, a direct thioetherification/amination reaction of thianthrenium salts is realized under metal-free conditions. This strategy exhibits good functional-group tolerance, operational simplicity, and an extensive range of compatible substrates.

Keywords

S-(alkyl) thianthrenium salts; meta-free; thioetherification; amination; functionalization of alcohol

Introduction

Sulfonium salts [1] have been extensively utilized as readily accessible synthetic building blocks in organic synthesis, particularly in the ipso-functionalization of C-S bonds. Of the sulfonium salts, organothianthrenium salts exhibit distinct structural properties and reactivities, thereby offering further potential in organic synthesis. Despite establishing a few preliminary methods for preparing organothianthrenium salts, their application potential is historically thwarted by harsh synthetic conditions and the poor durability of the resulting products [1g]. Recently, Ritter and co-workers have introduced a pioneering method for synthesizing air- and moisture-stable aryl thianthrenium salts [2]. This novel approach involves the utilization of tetra-fluorothianthrene sulfoxide (TFT=O) or thianthrene sulfoxide (TT=O), which react with arenes under mild conditions, exhibiting exclusive regioselectivity. Significant advancements in the synthesis of aryl thianthrenium salts have prompted a growing interest in their utilization as versatile precursors for the conversion of C-H bonds in arenes into C-C/X bonds through transition-metal-catalyzed cross-coupling processes [3]. On the other hand, sulfonium salts have emerged as appealing sources of aryl radicals for a wide range of transformations aimed at creating novel chemical bonds driven by their distinctive structural attributes and chemical tendencies (Scheme 1a) [1i, 4]. In addition to late-stage C-H functionalization of arenes, Wickens's group has introduced an oxidative alkene aziridination strategy that relies on thianthrenation of an alkene under electrochemical conditions [5]. Subsequently, cyclopropanation, [6] aziridination, [7] allylic C–H functionalization, [8] transition-metal catalyst cross-coupling9 and aminofunctionalization[10] of alkenes were achieved, benefiting from the unique reactivity of organothianthrenium species that are generated through the reaction of alkenes and thianthrene sulfoxide (TT=O) or thianthrene (TT) (Scheme 1b).



Scheme 1. Synthetic application of thianthrenium salts

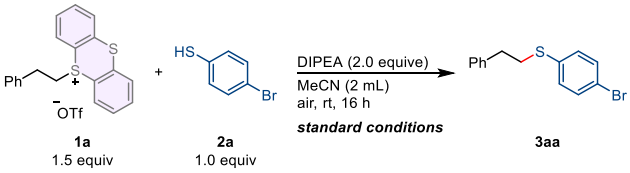
Alcohols are widely accessible and have significant importance in the pharmaceutical industry, positioning them as appealing candidates for C(sp^3) coupling due to their availability as a common chemical feedstock. However, due to the high bond dissociation energy of C-O bond and poor leaving ability of hydroxyl group [11], it is still a great challenge to transform alcohols into valuable chemicals [12]. A

recent study by Shi and co-workers has successfully converted alcohols into thianthrenium salts, enabling the transformation of the hydroxyl (OH) group into various functional groups via the photo-assisted generation of alkyl radicals [13]. After that, a series of methods for modification of alkyl thianthrenium salts have been developed, including the transition-metal catalyst cross-coupling with terminal alkynes [14], sulfonylation with DABCO·$(SO_2)_2$ [15], or alkylation of active alkenes [16]. Recently, Ritter and co-workers reported that alkyl thianthrenium salts can be employed to undergo reactions with N/O-nucleophiles under photocatalytic conditions [17]. Nevertheless, additional transition-metal catalysts, visible light, or electrochemical devices are required for the reported works. Therefore, developing a green method to functionalize alkyl thianthrenium salts is still highly desirable. Considering the highly polarized C(sp^3)–S bond in alkyl thianthrenium salts, alkyl thianthrenium salts have the potential to serve as alkyl electrophiles to react with nucleophiles directly in the absence of a metal catalyst [17].

Results and Discussion

With these considerations in mind, we investigated the possibility of the thioetherification between alkyl thianthrenium salts and thiophenols. After extensive screening of the reaction parameters, the desired thioetherification product **3aa** was obtained in 88% yield under the following optimal conditions: S-(alkyl) thianthrenium salt **1a** and 4-bromothiophenol **(2a)** as the model substrates, N,N-diisopropylethylamine (DIPEA) as the base, and added them to a vessel in air; after stirring for 16 hours at room temperature, the corresponding product was isolated by chromatographic purification in 88% yield (Table 1, entry 1). Reducing the amount of DIPEA gave diminished yield (Table 1, entry 2). Adding more base was unnecessary to get a higher yield (Table 1, entry 3). Subsequently, the use of other bases was not appropriate for promoting the generation of the thioetherification product **3aa** (Table 1, entries 4–7). Furthermore, the yields significantly varied (63−79%) depending on the different solvents (Table 1, entries 8–11).

Table 1. Optimization of the thioetherification of S-(alkyl) thianthrenium salt.[a]



Entry	Deviation from "standard conditions"	Yield of **2a** (%)[b]
1	none	88
2	1.5 equiv of DIPEA	73
3	3.0 equiv of DIPEA	85
4	NEt_3 instead of DIPEA	76
5	Na_2CO_3 instead of DIPEA	74
6	LiO^tBu instead of DIPEA	67
7	NaOH instead of DIPEA	71
8	toluene as solvent	63
9	DMF as solvent	67
10	THF as solvent	72
11	DCM as solvent	79

[a] Reaction conditions: all reactions were carried out using 1a (0.3 mmol), 2a (0.2 mmol), DIPEA (0.4 mmol) in 2.0 mL of MeCN at room temperature for 16 h under an air atmosphere. [b] Isolated yields after purification by column chromatography.

Having established the optimized reaction conditions, we assessed the range of

substrates suitable for this method. First, the scope of sulfonium salts was examined, as summarized in Scheme 2a. Alkyl sulfonium salts substituted with a halide (F, Cl, or Br) or cyano group at the para position of the aryl ring (**1b−1e**) were successfully converted into the carbon-sulfur bond formation products (**3ba–3fa**) in moderate to good yields. Even when sulfonium salt **1g** bearing a C(sp^3)-Br bond is susceptible to nucleophilic attack, the desired product **3ga** can still be obtained in good yield. Furthermore, substrate **1h** featuring two sulfonium salt motifs could undergo dual thioetherification at both reaction sites, resulting in the target product **3ha** in good yield. Secondary alkyl-substituted substrate **1i** underwent smooth thioetherification under the optimized reaction conditions, resulting the target product **3ia** in moderate yield. Next, we investigated the compatibility of various thiophenols with thianthrenium salt **1a** (Scheme 2b). When simple thiophenol **2b** was used as the substrate, good yield of the target product **3ab** was obtained smoothly. To our satisfaction, both electron-donating groups (Me, tBu, OMe; **2c−2e**) and electron-withdrawing groups (Cl and CF_3; **2f**, and **2g**) at the para position of the aryl ring of thiophenols were well tolerated, furnishing the desired products (**3ac−3ag**) in good yields. The reaction yield remains unaffected by the position of halon substituents (**2h−2j**), and the resulting products (**3ah−3aj**) can also be obtained with high efficiency. This underscores the viability of integrating this metal-free thioetherification method with other traditional cross-coupling reactions. Sterically hindered ortho-disubstituted thiophenol **2k** is also compatible with this reaction system, yielding the product **3ak** in good yield. Furthermore, heteroaromatic rings, such as pyridine (**2l**) thiophene (**2m**), benzoxazole (**2n**), and benzimidazole (**2o**), were all afforded the desired products (**3al−3ao**) in satisfactory yields.

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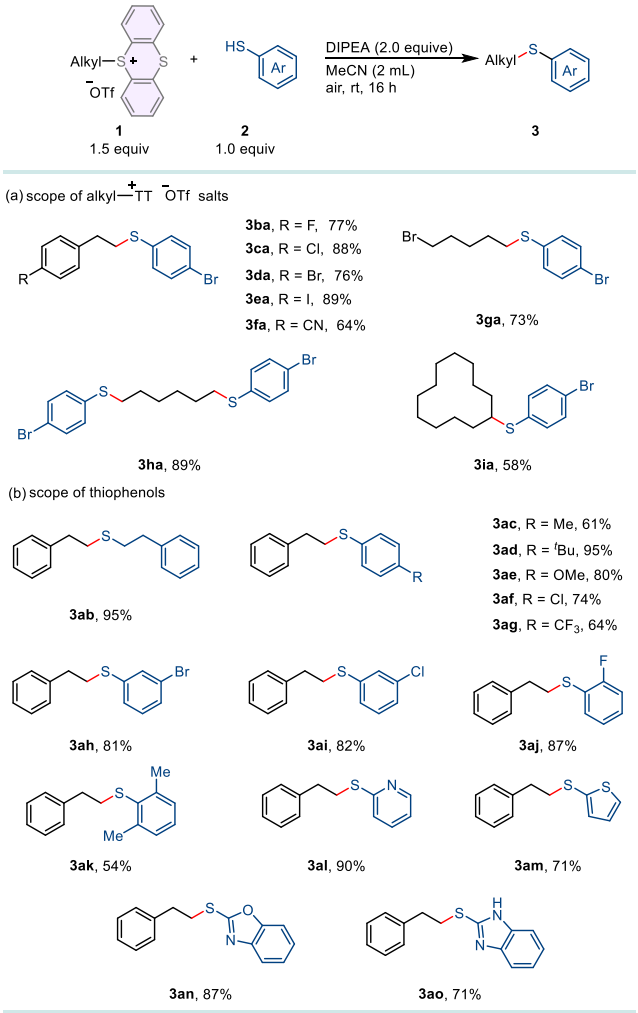
hindered ortho-disubstituted thiophenol **2k** is also compatible with this reaction system, yielding the product **3ak** in good yield. Furthermore, heteroaromatic rings, such as pyridine (**2l**) thiophene (**2m**), benzoxazole (**2n**), and benzimidazole (**2o**), were all afforded the desired products (**3al−3ao**) in satisfactory yields.

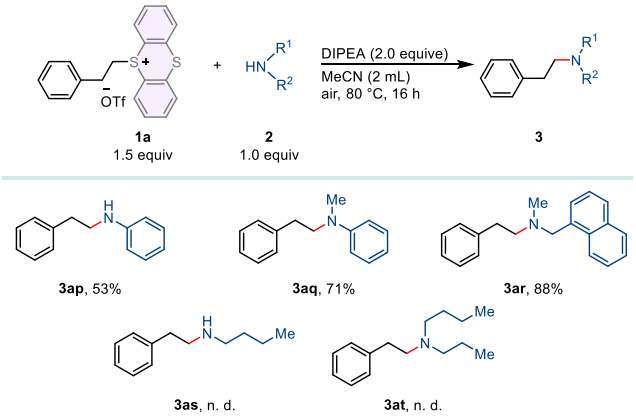
Scheme 2. Substrate scope.[a]



[a] Reaction conditions: alkyl thianthrenium salts **1** (0.3 mmol), thiophenols **2** (0.2 mmol), DIPEA (0.4 mmol) in 2.0 mL of MeCN at room temperature for 16 h under air atmosphere. Isolated yields.

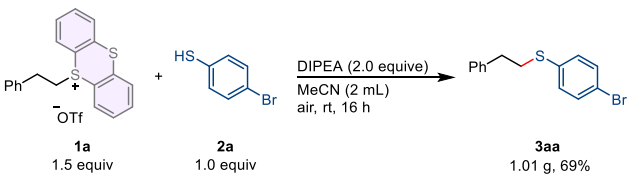
Subsequently, we investigated the substrate scope of amines, which is outlined in Scheme 3. To our delight, various amines (**2p–2r**), including aniline, N-methylaniline and benzylamine are also compatible under the optimal conditions to give the corresponding amination products (**3ap–3ar**) in moderate to high yields. For this amination method, it was necessary to investigate simple alkyl amines (**2s and 2t**) as the substrates. In doing so, we could not isolate the corresponding amination products **3as** and **3at**.

Scheme 3. Substrate scope of amines.[a]



[a] Reaction conditions: alkyl thianthrenium salts **1** (0.3 mmol), amines **2** (0.2 mmol), DIPEA (0.4 mmol) in 2.0 mL of MeCN at 80 ℃ for 16 h under air atmosphere. Isolated yields.

Scheme 4. Scale-up reaction.



To showcase the practical utility of our metal-free thioether formation process, we conducted a 5.0-mmol scale reaction and obtained the target product **3aa** in 69% yield (Scheme 4). This operationally simple protocol enables the rapid development of

novel thioetherification reactions using bench-stable alkyl thianthrenium salts as the electrophiles. As is well known, alkyl trifluoromethanesulfonate (alkyl-OTf), serving as a potent electrophilic reagent, can also engage in reactions with electrophilic reagents like thiophenol or amines under alkaline conditions, facilitating the formation of respective C-N/O bonds. The synthesis of alkyl thianthrenium salts requires alkyl trifluoromethanesulfonate as a precursor, which can also act as an electrophile. However, alkyl-OTf is prone to decomposition and poses challenges for storage at ambient temperature (for details, see the Supporting Information).

Conclusion

In summary, using the presented operational simple and metal-free method, we have synthesized thioether and amines from bench stable and readily available alkyl thianthrenium salts. Given the importance of alkyl thianthrenium salts in synthetic chemistry as alkyl reagents and the distinctive reactivities observed under photo/electrochemical conditions, we foresee significant opportunities emerging in the functionalization of alkyl thianthrenium salts using nucleophiles directly, without the need for external metal catalyst.

Supporting Information

Experimental procedures, characterization data for all new compounds, and NMR spectra of products (PDF)

Acknowledgements

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