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Sulfonium Salts Enable the Direct Sulfenylation of Activated C(sp^3)–H Bonds

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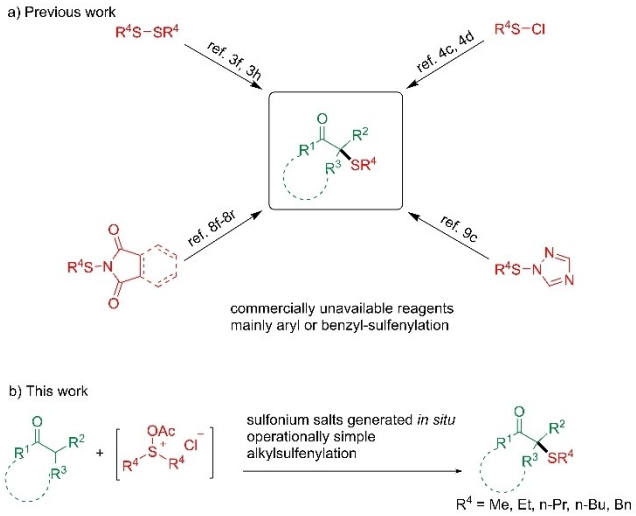
Herein, the direct α-sulfenylation of a series of β-dicarbonyl, β-ketophosphonate, and β-ketonitrile compounds, mediated by sulfonium salts has been described. Traditionally, sulfonium salts which are synthesized by activation of dialkylsulfoxides serve as oxidizing agents or precursors of sulfur ylide. In this transformation, sulfonium salts as readily prepared and operationally simple sulfenylation reagents firstly achieved alkylsulfenylation of various activated C(sp^3)–H bonds with the formation of tetra-substituted carbon center.

Introduction

Sulfur-containing compounds are privileged structural motifs found in natural products, pharmaceuticals, agrochemicals, and materials science.[1] Over the past few decades, considerable endeavors have been devoted to develop novel and efficient strategies for the formation of C–S bond. Among these methodologies, direct sulfenylation of C–H bond to form C–S bond is a concise and atom-economic approach which has attracted great attention from organic chemists. A variety of sulfenylation agents such as thiols,[2] disulfides,[3] arenesulfonyl/phenylsulfenyl chloride,[4] sulfonyl hydrazides,[5] sulfinic acids,[6] sodium sulfinates,[7] N-thioimides,[8] and triazole derivatives[9] have been employed in the formation of C–S bonds. Among them, α-sulfenylation of carbonyl compounds is especially attractive since these sulfenylated products are versatile building blocks and synthons in organic transformations.[10] However, traditional approaches mainly focused on using electrophilic sulfur reagents such as diaryldisulfides,[3f,h] phenylsulfenyl chloride,[4c,d] N-thioarylphthalimides,[8f–r] and triazole derivative[9c] to introduce a sulfur atom at α-position of carbonyl coumpounds (Scheme 1a). Despite some advantages and achieving enantioselective α-sulfenylation of carbonyl compounds, the exploitation of sulfenylation reagents which are easy to prepare or handle, inexpensive, commercially available, and performed under mild reaction conditions remains an unsolved problem. Furthermore, compared with aryl-or benzylsulfenylation reagents, alkylsulfenylation reagents are relatively rare.



Scheme 1. Sulfenylation of Carbonyl Compounds.

Sulfonium salts can be readily accessible by the activation of dialkylsulfoxides with electrophiles, which have traditionally been used as oxidizing agents or precursors of sulfur ylide. In this context, we utilized sulfonium salts generated *in situ* as sulfenylation reagents to realize the direct alkylsulfenylation of activated C(sp^3)–H bonds in β-dicarbonyl, β-ketophosphonate, and β-ketonitrile compounds under mild reaction conditions, providing the corresponding sulfenylated products with tetra-substituted carbon centers (Scheme 1b).

Results and Discussion

To start with, we selected β-ketoester **1a** and sulfoxide **2a** (DMSO) as the model substrates to optimize the reaction conditions, as shown in Table 1. Initially, **1a** reacted with sulfonium salt which was generated *in situ* by 1.5 equiv. DMSO activated with 1.5 equiv. oxalyl chloride in CH_3CN. Unfortunately, no sulfenylated products were obtained after 24 h (Table 1, entry 1). Then, the amount of DMSO was increased to 3.0 equiv, and the desired sulfenylation product **4a** was gained in 50% yield after 10 h (Table 1, entry 2). Subsequently, various electrophilic activators were screened, and a similar yield of **4a** was achieved with acetyl chloride as an activator (Table 1, entry 3–8). With the suitable activator in hand, we continued to amplify the amount of DMSO from 4.0 to 10.0 equiv. and maintained 1:2 ratio of acetyl chloride to DMSO (Table 1, entry 9–12). The results suggested that reaction time became

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Table 1. Optimization of Reaction Conditions.[a]

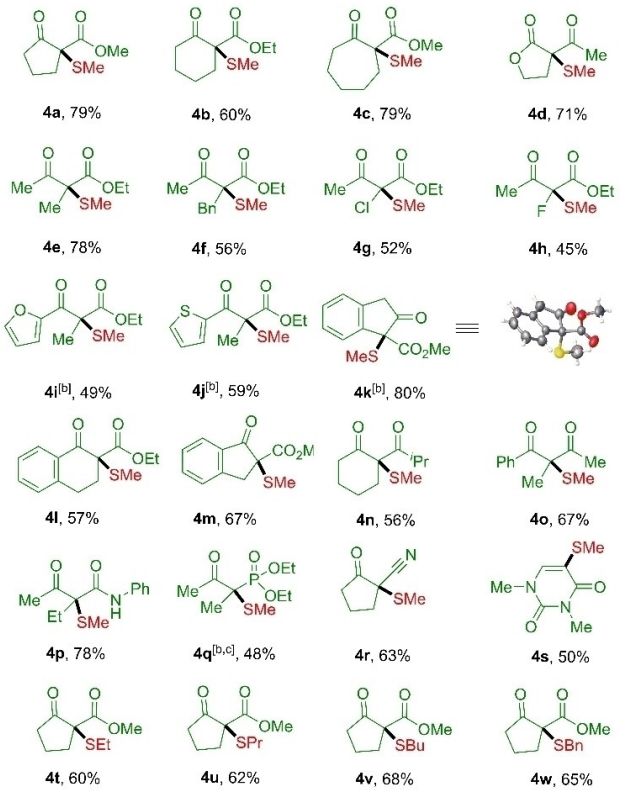
1a 2a 3 4a

Entry	Solvent	DMSO (equiv)	Activator	Time	Yield [%][b]
1[c]	CH_3CN	1.5	$(COCl)_2$	24 h	n.r.
2	CH_3CN	3.0	$(COCl)_2$	10 h	50
3	CH_3CN	3.0	AcCl	12 h	51
4	CH_3CN	3.0	BzCl	12 h	44
5	CH_3CN	3.0	TFAA	24 h	n.r.
6	CH_3CN	3.0	DCC	24 h	n.r.
7	CH_3CN	3.0	Tf_2O	24 h	20
8	CH_3CN	3.0	TfCl	24 h	n.r
9	CH_3CN	4.0	AcCl	8 h	55
10	CH_3CN	6.0	AcCl	3.5 h	60
11	CH_3CN	8.0	AcCl	2.5 h	79
12	CH_3CN	10.0	AcCl	2.0 h	79
13[d]	CH_3CN	12.0	AcCl	2.0 h	76
14	DCM	8.0	AcCl	3.0 h	66
15	toluene	8.0	AcCl	3.0 h	54
16	THF	8.0	AcCl	3.0 h	28
17	DMSO	8.0	AcCl	2.0 h	62
18[e]	CH_3CN	8.0	AcCl	24 h	42
19[f]	CH_3CN	8.0	AcCl	20 min	50
20[g]	CH_3CN	8.0	AcCl	3.5 h	68
21[h]	CH_3CN	8.0	AcCl	2.0 h	74
22[i]	CH_3CN	8.0	AcCl	25 min	76
23[j]	CH_3CN	8.0	AcCl	25 min	77
24[k]	CH_3CN	8.0	AcCl	25 min	79

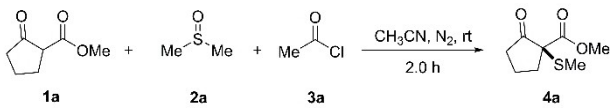
[a] Unless otherwise noted, all the reactions were carried out with **1a** (0.3 mmol), activator/DMSO = 1:2 in 0.5 mL solvent as indicated at room temperature. [b] Isolated yield. [c] $(COCl)_2$/DMSO = 1:1. [d] AcCl/DMSO = 1:3. [e] at 0 °C. [f] at 50 °C. [g] 1.0 mL of CH_3CN was used. [h] 0.3 mL of CH_3CN was used. [i] 2.0 equiv. $NaBF_4$ was added as additive. [j] 2.0 equiv. $NaPF_6$ was added as additive. [k] 2.0 equiv. $NaSbF_6$ was added as additive.

Table 2. Direct Sulfenylation of Activated C(sp^3)–H Bond.[a]

1 2 3 4



[a] Unless otherwise noted, all the reactions were carried out with **1** (0.3 mmol), **2** (2.4~6.0 mmol), **3** (1.2~3.0 mmol) in 0.5 mL CH_3CN at room temperature; for details, see the Supporting Information. [b] $NaSbF_6$ was added as additive. [c] oxalyl chloride was used as activator.

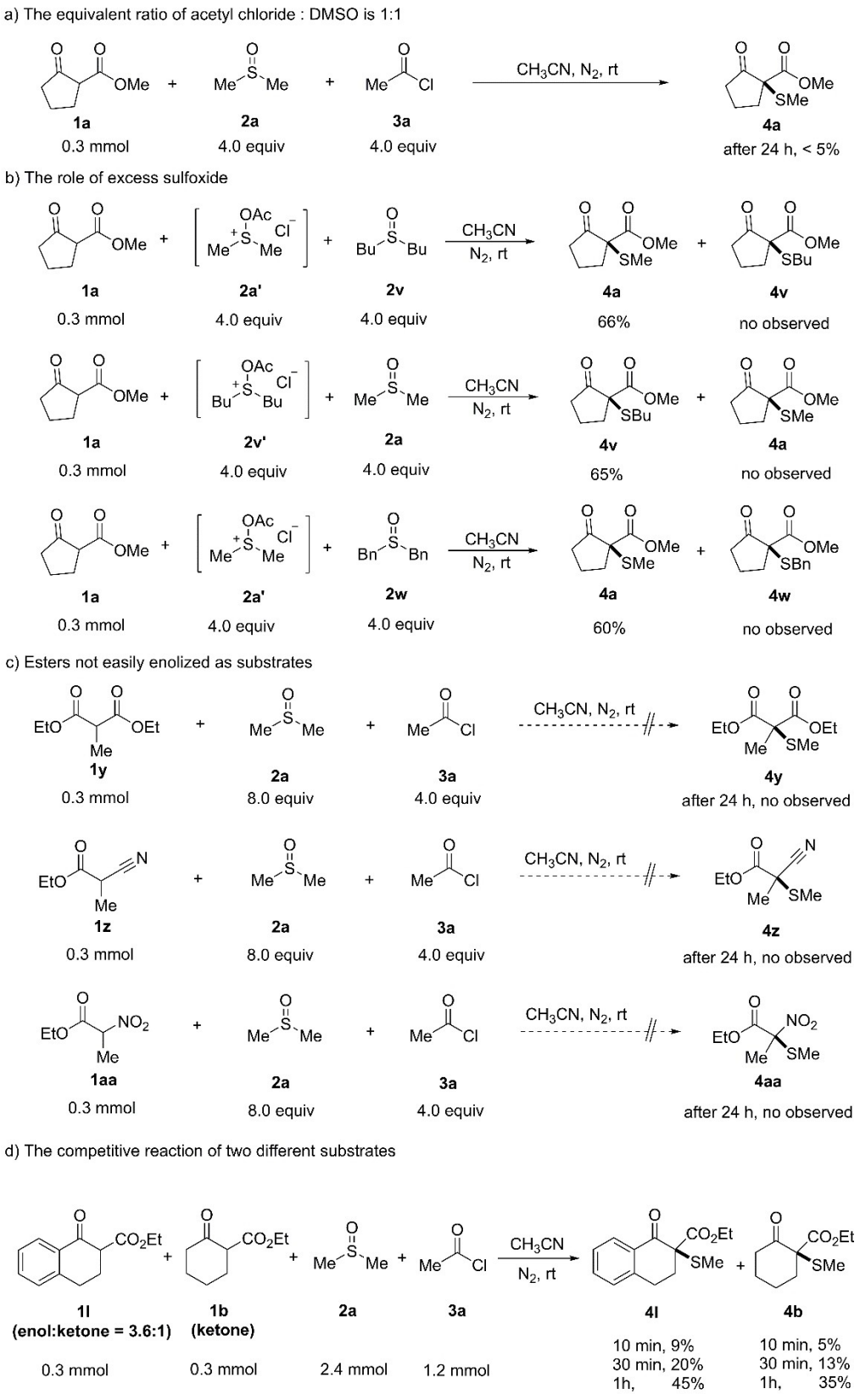


1a 12 mmol, 1.7 g scale 2a 3a 4a 73%, 1.66 g

Scheme 2. Gram-scale Synthesis.

shorter with an increasing amount of DMSO and acetyl chloride, and the highest yield of 79% was achieved when 8.0 equiv. DMSO was used (Table 1, entry 11). Then the ratio of acetyl chloride to DMSO was increased to 1:3, the desired product **4a** was acquired in a similar yield of 76% (Table 1, entry 13). Next, various solvents such as DCM, toluene, THF, and DMSO were investigated, and no further improvement in the yield was observed (Table 1, entry 14–17). Lowering reaction temperature resulted in a decrease in the yield of sulfenylated product **4a** and a prolonged reaction time (Table 1, entry 18). However, only 50% yield of **4a** was isolated at elevated reaction temperature (50 °C) with reduced reaction time (Table 1, entry 19). Variation of concentration did not improve the yield of **4a** further (Table 1, entry 20–21). According to previous reports,[11] addition of $NaSbF_6$ could increase the stability and reactivity of sulfonium ions. Additives such as $NaBF_4$, $NaPF_6$, and $NaSbF_6$ were added separately to the reaction system which not only maintained a high yield, but also dramatically accelerated the rate of this sulfenylation reaction (Table 1, entry 22–24).

To explore the generality of this transformation reaction, α-sulfenylation of a sequence of β-dicarbonyl, β-ketophosphonate, and β-ketonitrile compounds involving activated C(sp^3)–H bond was studied, and obtained corresponding products with tetra- substituted carbon center. As illustrated in Table 2, the aliphatic five to seven-membered ring β-ketoesters could be employed as successful substrates and the afforded sulfenylated products showed satisfactory yields (**4a**, **4b**, **4c**). Lactone-derived β-ketoesters also underwent the α-sulfenylation reaction well, and converted into the corresponding products with good yield (**4d**). Similarly, acyclic β-ketoesters bearing electron-donating groups (–Me, –Bn) and electron-withdrawing groups (–Cl, –F) at α-position could conduct the direct C–H bond methylthiolation and produce the expected products in moderate to good yield (**4e**, **4f**, **4g**, **4h**), of which electron-withdrawing groups (–Cl, –F) and more sterically congested group

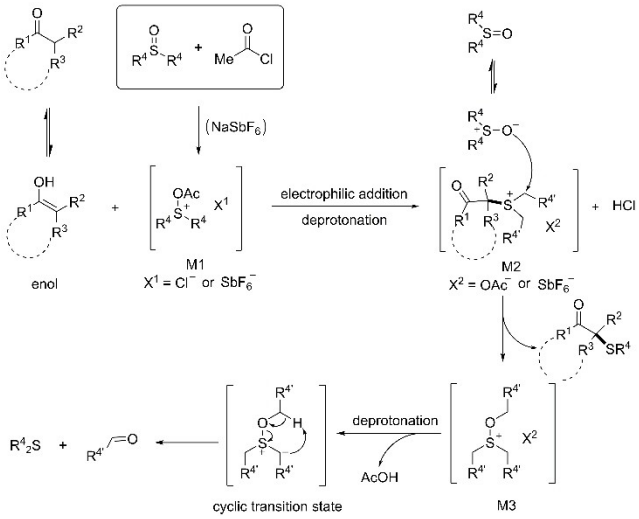


Scheme 3. Mechanistic Investigation.

(–Bn) at α-potision resulted in lower yields and longer reaction time. The reactivity of β-ketoesters derived from heteroaromatic furan and thiophene was also investigated, and the desired products were observed in moderate yields (**4i**, **4j**). Meanwhile, α-sulfenylation of β-ketoesters bearing aromatic ring also proceeded well under optimized reaction conditions to produce the products **4k**, **4l** and **4m**. The structure of **4k** was confirmed by single-crystal X-ray diffraction (CCDC 2021811).[12] Subsequently, cyclic and acyclic β-diketone compounds also can be employed as effective substrates to produce the sulfenylated products **4n** and **4o**. Notably, β-keto amide, β-keto phosphonate and β-ketonitrile compounds were all tolerated in this sulfenylation transformation (**4p**, **4q**, **4r**). This methodology also successfully incorporated methylthio group into dimethyluracil with promising biological activities (**4s**). Further investigation of different types of sulfonium salts revealed that diethyl sulfoxide, dipropyl sulfoxide, dibutyl sulfoxide, and dibenzyl sulfoxide-derived sulfonium salts all could be compatible in this sulfenylation transformation and generated the desired products in good yields (**4t**, **4u**, **4v**, **4w**). However, sulfonium salts derived from diaryl sulfoxides and arylalkylsulfoxides were not accommodated under the optimized reaction conditions and afforded α-chlorinated products (see supporting information for details). To illustrate the synthetic utility of this transformation, we conducted a gram-scale reaction using 1.7 g of **1a** as starting material to produce the desired product **4a** in 73% (1.66 g) yield (Scheme 2).

To provide some insight into this sulfenylation process, several control experiments were conducted to illustrate the reaction pathway (Scheme 3). When the equivalent ratio of acetyl chloride to DMSO is 1:1, product **4a** was not observed after 24 h, suggesting excess sulfoxide played an indispensable role in this transformation (Scheme 3a). Under the standard reaction conditions, we performed the sulfenylation reaction with **1a**, sulfonium salt **2a'** generated *in situ* and excess sulfoxide **2v** as substrates, only product **4a** was obtained in 66% yield, and no product **4v** was observed. Similar two experiments were also conducted, and identical results were obtained (Scheme 3b). This excluded the existence of disulfonium salts which were synthesized by nucleophilic substitution of excess sulfoxide to sulfonium salt formed initially, and illustrated that substrate **1a** firstly reacted with sulfonium salts generated *in situ*, and then further reacted with excess sulfoxide to acquire the desired products. Subsequently, we used esters which contained electron-withdrawing group at α-position as substrates, such as **1y**, **1z**, and **1aa** which were not easy to enolize. No sulfenylated products were observed after 24 h under the standard reaction conditions (Scheme 3c). Furthermore, an intermolecular competitive reaction between substrates **1l** and **1b** was conducted, and product **4l** was obtained with a higher yield than **4b** at the same reaction time (Scheme 3d). This observation can be ascribed to substrate **1l** which mainly exists in enol form reacts faster with sulfonium ions than **1b** which exists in keto form, indicating that substrates transformed from ketone to enol.

Based on the above mechanistic investigation and previous reports,[11,13] a plausible reaction pathway is shown in Scheme 4,



Scheme 4. Proposed Reaction Pathway.

sulfoxide is firstly treated with activator acetyl chloride to form sulfonium salt M1, which could improve its reactivity and the reaction rate can be accelerated by the addition of $NaSbF_6$. After enolization of carbonyl compound, electrophile M1 undergoes electrophilic addition and deprotonation with enol compounds, leading to the formation of intermediate M2 with concomitant expulsion of hydrogen chloride. Subsequently, nucleophilic attack of excess sulfoxide takes place at carbon center adjacent to cationic sulfur, resulting in the formation of the desired product and new intermediate M3. Finally, M3 is transformed into corresponding dialkyl sulfide and aldehyde via deprotonation and cyclic transition state.

Conclusions

In summary, we have developed a novel strategy which enables the direct installation of alkylthio group into α-position of a series of β-dicarbonyl, β-ketophosphonate, and β-ketonitrile compounds using sulfonium salts generated *in situ* as sulfur sources. This work not only provides a simple methodology for the synthesis of α-sulfenylated carbonyl compounds with tetrasubstituted carbon center but further extends the application scope of sulfonium salts.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–S bonds · β-Dicarbonyl compounds · Sulfenylation · Sulfonium salts · Sulfoxides

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[12] Deposition Number 2021811 (for **4k**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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