

Intermolecular Sulfenoamination of Alkenes with Free-Thiols and NIS to Access β -Succinimide Sulfides

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A convenient and practical multicomponent strategy for the sulfenoamination of alkenes was realized, which using free-thiols as the sulfur-reagent, NIS both as radical initiator and an N-nucleophile. This protocol excellent in terms of transition-

metal-free, good functional group tolerance, easily available substrates and facile scale-up. And provided a direct- and general way to synthesize various β -succinimide sulfides with high regioselectivity.

Introduction

Organosulfur compounds are a class of crucial molecules that have broad use in the pharmaceuticals, agrochemicals and functional materials, owing to their remarkable biological activities and distinctive photochemical properties.^[1,2] Among them, the β -amino sulphides, such as commercially approved drugs Amoxicillin,^[3] Viracept,^[4] Apremilast^[11] and Butoconazole^[5] (Figure 1) have drawn considerable attentions. Consequently, the synthetic pursuit of β -amino sulfides attractive among chemists in both academic and industry.

Olefins are recognized as simple and abundant feedstocks, and their regioselective 1,2-difunctionalization plays a crucial role in rapidly broadening molecular complexity by introducing two functional groups simultaneously.^[6–8] In this regard, the sulfenoamination of alkenes has emerged as an ideal strategy for the synthesis of β -functionalized sulfides, which have drawn much attention in chemical synthesis.^[9–11] Specifically, several methods for the intramolecular sulfenoamination using *N*-alkenyl sulfonamides as substrates have been well investigated to prepare *N*-heterocyclic sulfides.^[9] In addition, the intermolecular sulfenoamination would be a general and economic manner to construct β -amino sulfides. For instance, Denmark *et al.* reported the metal-free Ritter-type protocol of alkenes to provide β -acetamido sulfides (Figure 2a).^[12–14] An alternative method for the synthesis of β -amino sulfide derivatives from oxiranes, PhSNa, and nitrile has also been developed (Figure 2b).^[15,16] In 2022, Zhong's group reported a photoredox-neutral approach for the three-component thioamination of vinylarenes towards valuable vicinal *N,S*-disubstituted molecules (Figure 2c).^[17] However, most of these reactions often limited to prefunctionalized thiolating reagents, harsh reaction conditions, poor substrate scope, lower regioselectivity, or toxic metal

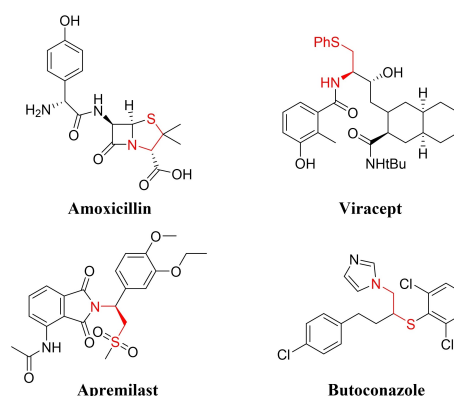


Figure 1. Drugs containing β -amino sulfide motifs.

catalysts. Thus, it is highly desirable to develop efficient and general synthetic methods to construct β -amino sulfides.

N-iodosuccinimide (NIS) was used as a source of iodine in various electrophilic radical reactions.^[18–20] Meanwhile, NIS-promoted difunctionalization of alkenes became very attractive. In 2023, Deng and co-workers reported a multicomponent amidosulfenylation of alkenes by using NIS with disulfides (Figure 2d).^[21] As part of our research work aimed at the construction of C–S, N–S bonds.^[22,23] Herein, a direct difunctionalization protocol of alkenes was disclosed, by employing free-thiols as thiolating source and NIS as *N*-nucleophile and radical agent under mild conditions.

Results and Discussion

Initially, styrene **1a** and 4-fluorophenylthiophenol **2a** were specifically chosen as model substrates to optimize the reaction conditions (Table 1). As expected, the reaction proceeded smoothly to afford target product **3aa** in 81% isolated yield with sodium persulfate as the oxidant (entry 1). Investigations of the reaction solvents showed that DCE was more suitable for this transformation than other solvents (entries 2, 3), and no desired product was detected when the reaction was performed with H₂O, EtOH, THF, DMSO as solvent (entry 3). As shown, the desired product was decreased sharply when the

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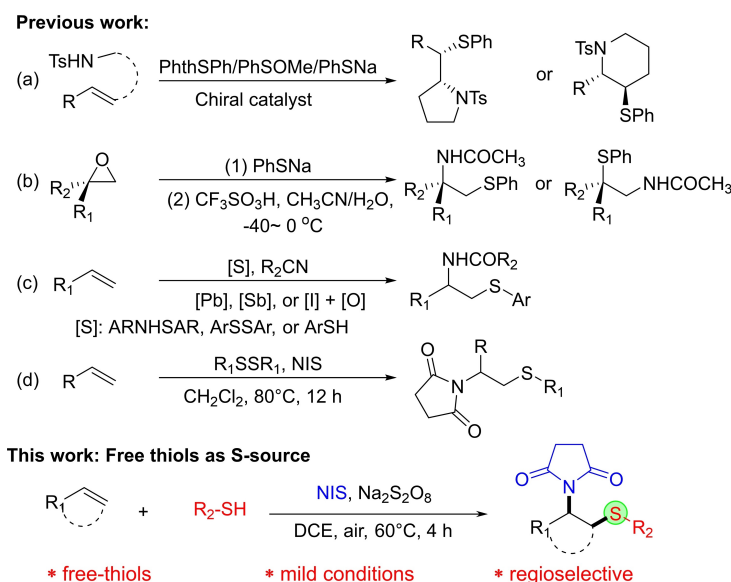


Figure 2. Synthetic routes of β -amino sulphides.

Table 1. Selected optimization conditions.^[a]

Entry	Variation from the standard conditions	Yield ^[b]
1	None	81
2	DCM, CHCl ₃ , MeCN as solvent	53, 18, 12
3	H ₂ O, EtOH, THF, DMSO as solvent	nd
4	(NH ₄) ₂ S ₂ O ₈ , <i>m</i> -CPBA, H ₂ O ₂ instead of Na ₂ S ₂ O ₈	64, 20, trace
5	0, 0.25, 1.0 eq. Na ₂ S ₂ O ₈	Trace, 60, 68
6	NCS, NBS, instead of NIS	Trace
7	Succinimide instead of NIS	nd
8	rt, 40 °C, 80 °C instead of 60 °C	24, 55, 78
9	1 h, 2 h, 6 h instead of 4 h	37, 56, 80
10	Under N ₂ atmosphere	78

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), **2a** (0.4 mmol, 2.0 eq.), NIS (0.4 mmol, 2.0 eq.), Na₂S₂O₈ (0.1 mmol, 0.5 eq.), DCE (4.0 mL), in air, 60 °C 4 h. [b] Isolated yield. nd: not detected.

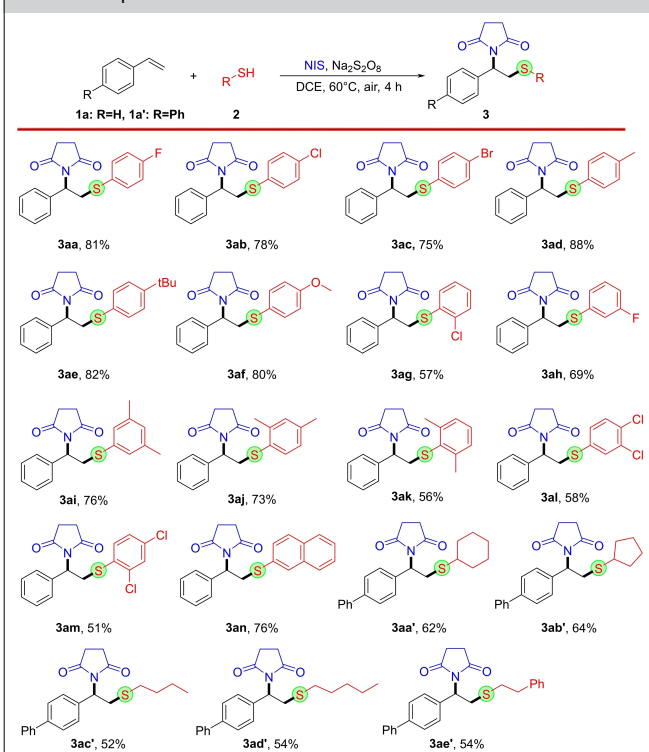
Na₂S₂O₈ was replaced by (NH₄)₂S₂O₈, *m*-CPBA or H₂O₂ (entry 4). Further controls demonstrated that increase or decrease the amount of Na₂S₂O₈ was not suitable for this protocol (entry 5). Remarkably, the replacement of NIS with other succinimide derivatives (NCS, NBS) significantly impacted the reaction yield (entry 6), no desired product was observed in the presence of succinimide and I₂ (entry 7). Subsequent investigation on the effect of the reaction temperature proved that 60 °C was appropriate for this protocol (entry 8). The reaction time has a remarkable effect on the preparation of the ideal product **3aa**, and shorten reaction time gave a much poor yield (entry 9). A

slightly decreased yield of 78% was observed when the reaction was conducted under N₂ atmosphere (entry 10).

After optimizing the reaction conditions, the scope of thiols was firstly explored and summarized in Tables 2. Notably, aryl thiols featuring weak electron-withdrawing or electron-donating groups, such as 4-chloro, 4-bromo, 4-*t*-butyl (**2d**), and 4-methyl yielded the target products (**3ab–3ae**) in excellent yields (75%–88%). Additionally, the 4-methoxythiophenol (**2f**) bearing a strong electron-donating group could afford the relatively product **3ab** in 80% yield. However, derivatives like 4-(trifluoromethyl)thiophenol and 4-nitrothiophenol did not provide the desired products. It suggested that excessively strong electron-withdrawing substituents on the aryl ring will hinder the reaction, while strong electron-donating ones may not. When thiophenols containing halogens at the *meta*- or *ortho*-position were employed, the target products **3ag** and **3ah** were obtained in moderate yields (57%–69%). Moreover, the reaction exhibited compatibility to polysubstituted aryl thiols, 3,5-dimethylthiophenol (**2i**), 2,4-dimethylthiophenol (**2j**), 2,6-dimethylthiophenol (**2k**), 4,5-dichlorothiophenol (**2l**), and 2,4-dichlorothiophenol (**2m**) produced satisfactory products **3ai–3am** with 51%–76% yields. It further showed that 2,4,6-triisopropylthiophenol was not successfully scaled up to the target product, indicated that steric hindrance effect was not favourable to this progress. To our delight, replaced the phenylthiol with a polyaromatic ring like 2-naphthalenyl thiol was applicable to the reaction, resulted **3an** in 73% yield. Significantly, a variety of aliphatic thiols, such as cyclohexanethiol (**2a'**), cyclopentanethiol (**2b'**), *n*-butanethiol (**2c'**), *n*-pentanethiol (**2d'**) and 2-phenylethanethiol (**2e'**) were also amenable, afforded the desired products (**3aa'–3ae'**) with 52%–62% yields.

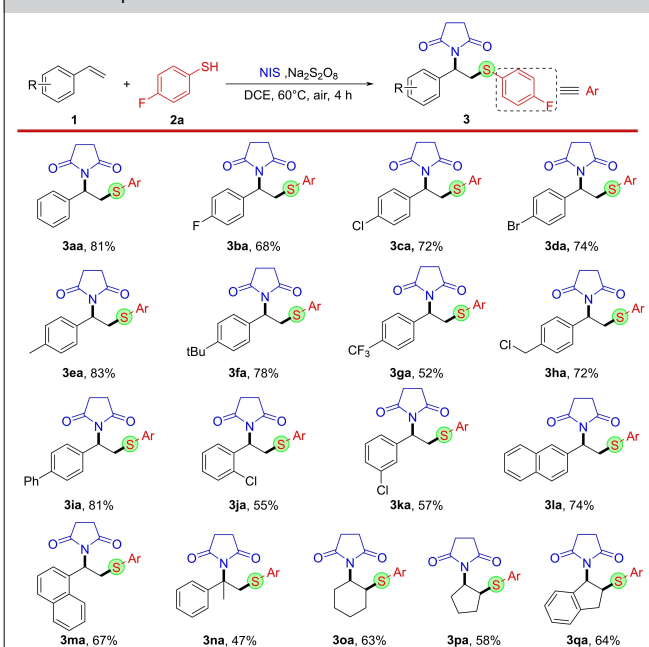
Subsequently, the scope with respect of alkenes was also explored (depicted in Table 3). Initially, a range of styrenes with weakly electron-withdrawing or -donating groups on the

Table 2. Scope of the thiols.^[a]



[a] Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), **2** (0.4 mmol, 2.0 eq.), NIS (0.4 mmol, 2.0 eq.), Na₂S₂O₈ (0.1 mmol, 0.5 eq.), DCE (4.0 mL), in air, 60 °C 4 h.

Table 3. Scope of the alkenes.^[a]

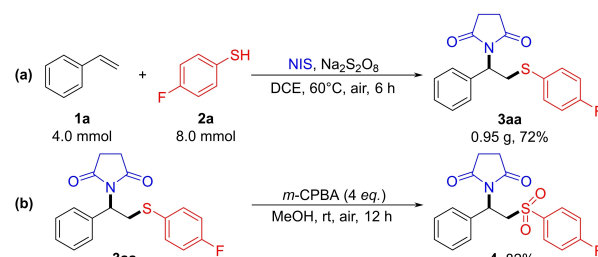


[a] Reaction conditions: **1** (0.2 mmol, 1.0 eq.), **2a** (0.4 mmol, 2.0 eq.), NIS (0.4 mmol, 2.0 eq.), Na₂S₂O₈ (0.1 mmol, 0.5 eq.), DCE (4.0 mL), in air, 60 °C 4 h.

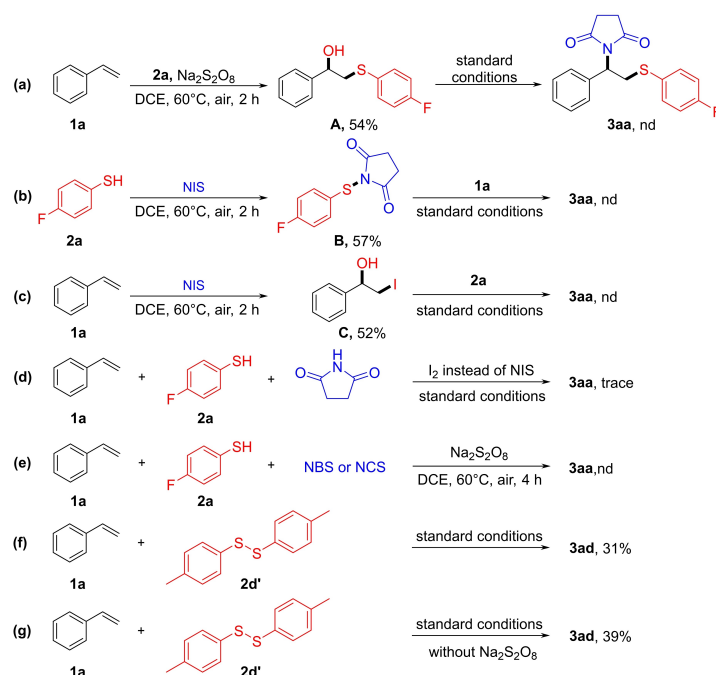
aromatic ring proceeded well under the optimized conditions, gave the desired products **3ba–3fa** in moderate to excellent yields. Notably, 4-trifluoromethylstyrene yielded the target product **3ga** with a 52 % yield, whereas 4-methoxystyrene was failed to generate the target product. Besides, 4-(chloromethyl)styrene and p-phenylstyrene were well-tolerated, transformed to the corresponding products (**3ha**, **3ia**) smoothly. When 2-chlorostyrene (**1j**) and 3-chlorostyrene (**1k**) were utilized in the reaction, the target products **3ja** and **3ka** were obtained in moderate yields (55%–57%). Compared among **3ca**, **3ja** and **3ka**, a steric hindrance effect on the reaction was detected. As delighted, the 2-naphthylethylene and 1-naphthylethylene were applicable to the reaction, accomplished the desired products **3ma** and **3na** with 74%, 67% yields, respectively. Noteworthy, the sulfenoamination reaction proceeded well when more bulk prop-1-en-2-ylbenzene was used, and produced **3na** in 47% yield. Furthermore, cyclic alkenes, such as cyclohexene, cyclopentene and indene were also suitable for the reaction and gave the corresponding products (**3oa–3qa**) in moderate yields (58%–64%). Unfortunately, no relative product was observed when using linear aliphatic alkene as starting material.

In order to further illustrate the potential applicability of this directly sulfenoamination of alkenes with free-thiols. The gram-scale synthesis was performed on a 4.0 mmol scale, and 0.95 g of the desired product **3aa** was isolated in 72% yield. It was slightly lower than the previous yield of 81% (Scheme 1a). Subsequently, the sulfide moiety of **3aa** could be oxidized by *m*-CPBA to give sulfone **4** in 82% yields (Scheme 1b). These results demonstrated its potential in practical synthesis of β -amino sulfides and their derivatives.

In order to investigate the possible mechanism of this 1,2-difunctionalization protocol, a series of control experiments were conducted (Scheme 2). Initially, β -hydroxy sulfide **A** was obtained with 54% yield in the absence of NIS. Then, further reacting of compound **A** under standard conditions was attempted, and no desired product was obtained, implied that β -hydroxy sulfide **A** may serve as a by-product or an unreacted intermediate in this process (Scheme 2a). In addition, to identify the intermediates of this protocol, *N*-arylsulfonyl succinimide **B** and β -hydroxy iodide **C** were isolated with 57% and 52% yields, respectively. However, further reaction of both compounds **B** and **C** did not lead to the corresponding product **3aa** (Scheme 2b and c). Moreover, no desired product **3aa** was obtained when NIS was replaced by I₂, NBS or NCS, suggested



Scheme 1. Gram-scale synthesis and synthetic application.



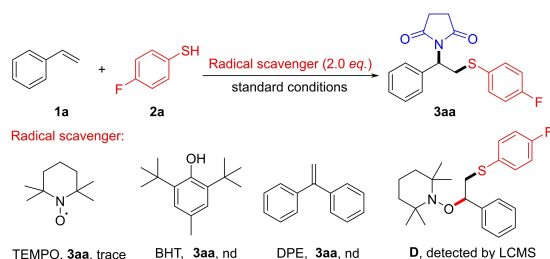
Scheme 2. Control experiments.

that NIS as an indispensable agent in the reaction (Scheme 2d and e). At last, replaced *p*-toluene thiophenol with *p*-toluene disulfide under the standard conditions or without $\text{Na}_2\text{S}_2\text{O}_8$, the target product **3ad** was isolated in 31% and 39% yield respectively (Scheme 2f and g), which were much lower than that of *p*-toluene thiophenol (88%). It suggested that disulfide was not a key intermediate in this protocol and may partly involved in the reaction.

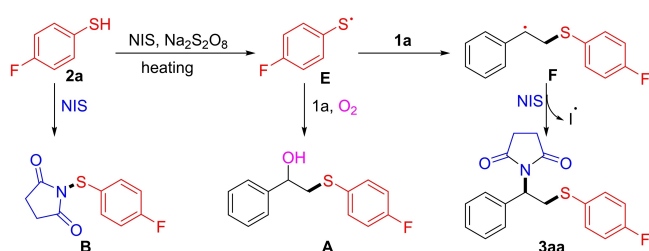
In addition, the standard reaction was dramatically inhibited by adding the radical scavengers, including 2,2,6,6-tetramethyl-

piperidin-1-oxyl (TEMPO), butylated hydroxytoluene (BHT), or 1,1-diphenylethene (DPE), which indicated the potential of a free radical pathway in this protocol (Scheme 3). As delighted, the TEMPO trapped adduct **D** was detected by LC-MS simultaneously.

Based on the experimental findings and literature references,^[21,24,25] a plausible reaction mechanism was proposed in Scheme 4. Initially, a sulfur radical intermediate **E** was generated from **2a** under the combine influence of $\text{Na}_2\text{S}_2\text{O}_8$, NIS and heating. Subsequently, the radical **E** was reacted with **1a** to form the intermediate **F**. Finally, the NIS nucleophilic attacked radical intermediate **F** to afford final product **3aa** and regenerate the iodine radical, which formed I_2 and succinimide radical for the radical propagation. By the way, the β -hydroxy sulfide **A** was yield via the thiol-olefin co-oxidation of intermediate **E** with oxygen. Additionally, **2a** could react with NIS to produce the by-product *N*-arylsulfonyl succinimide **B**.



Scheme 3. Free radical trapping experiments.



Scheme 4. Proposed mechanistic pathway.

Conclusions

In conclusion, an efficient sulfenoamination of alkenes with free-thiols and NIS was developed. This switchable approach features mild and environmental friendly reaction conditions, a broad substrate scope, and un-prefunctionalized thiols as sulfonylation reagents. Notably, the NIS played both as a promoter and an *N*-nucleophile in this protocol. It also highlighted in terms of facile scale-up and functional groups tolerance in air atmosphere. Preliminary mechanistic studies support a radical pathway. Further study and synthetic application of this sulfenoamination progress are underway.

Author Contributions

W. Chen and R. Wu conceived and designed the study; R. Wu, W. X. Wang, H. P. Zhou and P. B. Yu performed the synthetic experiments and analyzed the data for all compounds; W. Chen, W.X. Wang and R. Wu co-wrote the paper.

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Conflict of Interests

There are no conflicts to declare.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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