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Cite this: *Org. Biomol. Chem.*, 2025, **23**, 2439

NBS-promoted regioselective thiocyanatothioloation of alkenes with free thiols and NH_4SCN †

Wei Chen, * Run Wu, Wanxiang Wang, Haiping Zhou and Mingyue Fu

Received 13th December 2024,
Accepted 27th January 2025

DOI: 10.1039/d4ob02020k

rsc.li/obc

An efficient NBS-promoted three-component thiocyanatothioloation of alkenes with free thiols and NH_4SCN has been developed. This protocol avoids tedious preactivation of thiols and employs a diverse range of accessible thiols directly as sulfur sources. Moreover, the reaction exhibits regioselectivity and shows high compatibility with styrenes and unactivated alkenes. Preliminary mechanism studies revealed that both a radical pathway and thiol-oxidation-coupling were involved in this protocol.

Introduction

Sulfur-containing molecules are ubiquitous structural motifs, and are prevalent in natural products,¹ pharmaceuticals,² agrochemicals³ and materials owing to their distinctive pharmacological and characteristic photochemical properties⁴ (Fig. 1). Among them, thiocyanates constitute an important class of compounds used as antiproliferatives⁵ and HIV inhibitors,⁶ which also serve as key intermediates for the preparation of thioethers,⁷ trifluoromethyl sulfides,⁸ heterocycles,⁹ etc. Consequently, extensive work has been devoted to devising novel and efficient methods for the incorporation of S-moieties into organic compounds.¹⁰ The ability to introduce different sulfur-containing functional groups into the target molecules simultaneously for the assembly of diverse frameworks is particular importance.¹¹

Multicomponent reactions are considered to be suitable methods for achieving the goal of step and energy economy. In 2010, Zefirov's group reported the disulfonation of unsaturated compounds with ethyl benzenesulfonate and trimethylsilyl isothiocyanate under a N_2 atmosphere (Scheme 1a).¹² Meanwhile, Xiao and Fu developed a regio- and stereo-selective difunctionalization of alkenes by using *N*-thiosuccinimides (Scheme 1b and c).¹³ It was noted that the previous strategies typically required the preactivation of thiols and substantially limited substrates. Despite these significant advances, thiocyanatothioloation of alkenes directly from easily available free thiols and NH_4SCN has not been reported, and it is challenging to control the chemo- and regio-selectivity of these two nucleophiles at once.

As a continuation of our interest in exploring novel protocols for the formation of C–S and N–S bonds,¹⁴ here we report an efficient and regiocontrollable difunctionalization of alkenes with free thiols and NH_4SCN under mild conditions, including activated aryl alkenes, and non-activated aliphatic alkenes with diverse alkyl/aryl-thiols (Scheme 1d).

Results and discussion

Initially, styrene (**1a**), NH_4SCN (**2a**), and 4-fluorothiophenol (**3a**) were chosen as model substrates to optimize the reaction conditions. To our delight, the model reaction was conducted smoothly in MeCN (4.0 mL) with NBS (0.4 mmol, 2.0 eq.), and the desired β -thiocyanate sulfide **4aa** was isolated in 86% yield within 30 min (Table 1, entry 1). Changing the solvent to MeOH or THF dramatically decreased the production of **4aa** (Table 1, entries 2 and 3). The use of 1,4-dioxane led to no desired product being detected (Table 1, entry 4). When the

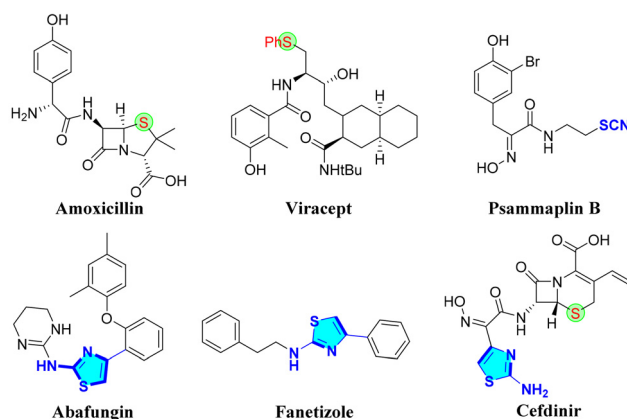
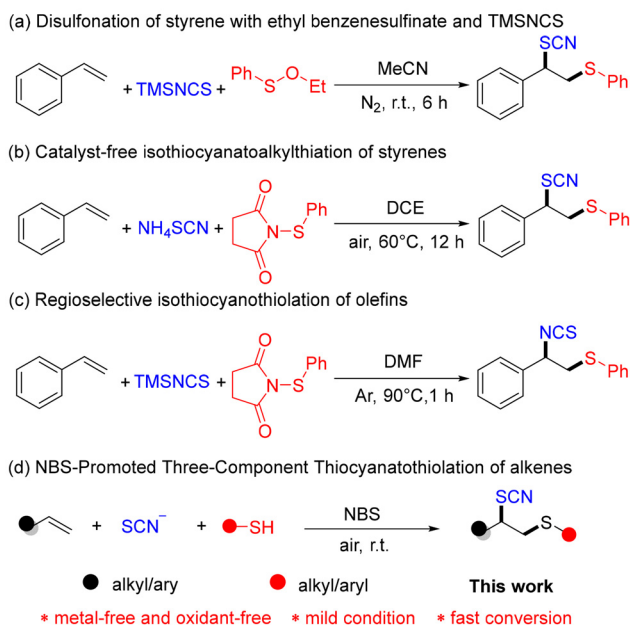


Fig. 1 Representative examples of sulfur-containing molecules.

Sichuan Engineering Research Center for Biomimetic Synthesis of Natural Drugs, School of Life Science and Engineering, Southwest Jiaotong University, Chengdu, 610031, China. E-mail: chenweicstq@163.com

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4ob02020k>

Previous work:



Scheme 1 Methods for (iso)thiocyanatothiolation of alkenes.

Table 1 Selected optimization conditions^a

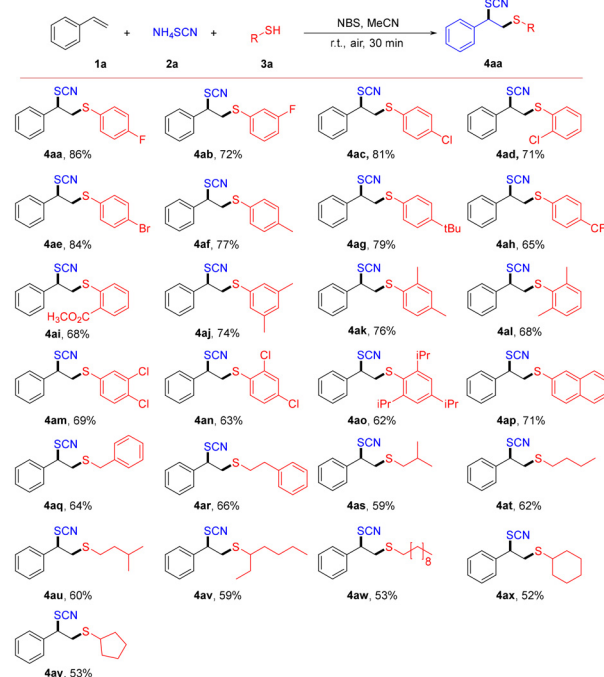
Entry	Variation from the standard conditions	Yield ^b
1	None	86
2	MeOH as solvent	23
3	THF as solvent	19
4	1,4-Dioxane as solvent	n.d.
5	H ₂ O as solvent	24
6	MeCN/H ₂ O (v/v = 4 : 1) as solvent	42
7	MeCN/H ₂ O (v/v = 20 : 1) as solvent	64
8	1.0, 1.5 eq. of NBS	19, 57
9	NCS, NIS instead of NBS	n.d.
10	No NBS	n.d.
11	1.5 eq. of 2a	74
12	1.0 eq. of 3a	68
13	5, 15, 60 min instead of 30 min	52, 75, 83
14	40, 60, 80 °C instead of r.t.	70, 56, 44
15	Under N ₂ atmosphere	68

^a Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), **2a** (0.24 mmol, 1.2 eq.), **3a** (0.4 mmol, 2.0 eq.), NBS (0.4 mmol, 2.0 eq.), MeCN (4.0 mL), in air, room temperature, 30 min. ^b Isolated yields. n.d. = not detected.

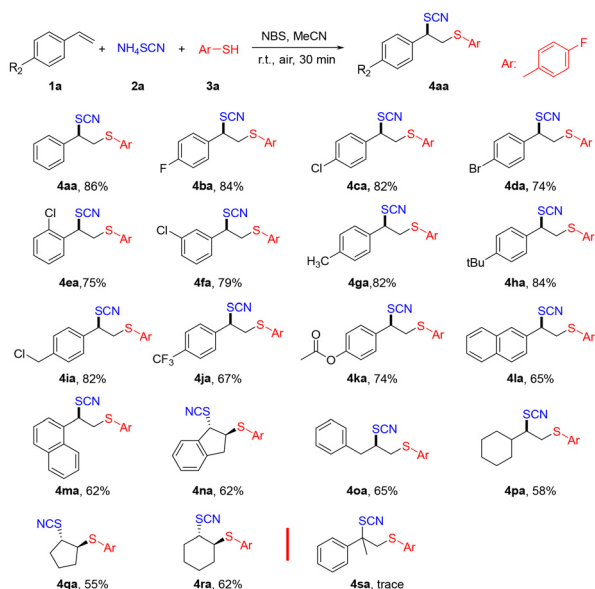
green solvent water was used, only a 24% yield of **4aa** was obtained (Table 1, entry 4). To our delight, increasing the proportion of MeCN in the mixed solvent of MeCN/H₂O significantly improved the production of **4aa** (Table 1, entries 6 and 7), further indicating that MeCN is the optimal solvent in this protocol. Decreasing the amount of NBS to 1.0 eq. or 1.5 eq. resulted in much poorer yields of **4aa** (19% and 57%, respec-

tively; Table 1, entry 8). None of the product **4aa** was detected when NBS was replaced by NCS or NIS (Table 1, entry 9). As expected, no conversion was observed without NBS (Table 1, entry 10). The control experiments confirmed the necessity of NBS in this protocol. Increasing the **2a** loading or decreasing the **3a** loading led to a slightly diminished yield of **4aa** (Table 1, entries 11 and 12). Neither increasing nor decreasing the reaction time could improved the production of **4aa** (Table 1, entry 13); thus, 30 min was selected as the optimal reaction time to selectively afford the desired **4aa** with 86% yield. Additionally, increasing the temperature from room temperature to 80 °C resulted in a lower yield (Table 1, entry 14). It is noteworthy that only 68% yield of **4aa** was obtained under a nitrogen atmosphere (Table 1, entry 15).

With the optimized conditions, an exhaustive exploration of the substrate scope was carried out, as summarized in Schemes 2 and 3. Initially, a series of substituted thiophenols with both weakly electron-withdrawing and electron-donating groups (such as 2-fluoro (**4ab**), 4-chloro (**4ac**), 2-chloro (**4ad**), 4-bromo (**4ae**), 4-methyl (**4af**) and 4-*tert*-butyl (**4ag**)), efficiently produced the desired products in 77–84% yields. Notably, trifluoromethyl (**4ah**) and methoxycarbonyl (**4ai**) were well tolerated under the standard conditions. Multisubstituted thiophenols were also smoothly transformed into the corresponding products (**4ag–4ao**). This indicated that steric factors do not play a role, whether the substituents are in the *ortho*-, *meta*- or *para*-position. In addition to thiophenol derivatives, this protocol was applicable to thionaphthol (**4ap**). Fortunately, benzyl thiol (**4aq**), 2-phenylethanethiol (**4ar**), and various linear and



Scheme 2 Thiophenol substrate scope. Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), **2a** (0.24 mmol, 1.2 eq.), **3a** (0.4 mmol, 2.0 eq.), NBS (0.4 mmol, 2.0 eq.), MeCN (4.0 mL), under air, room temperature, 30 min.



Scheme 3 Alkene substrate scope. Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), **2a** (0.24 mmol, 1.2 eq.), **3a** (0.4 mmol, 2.0 eq.), NBS (0.4 mmol, 2.0 eq.), MeCN (4.0 mL), under air, room temperature, 30 min.

nonlinear aliphatic thiols (**4as–4ay**) were also amenable, affording the respective products with moderate to good yields. Unfortunately, 4-nitrothiophenol, 4-methoxythiophenol and 2-benzothiazolethiol were not effective in this protocol.

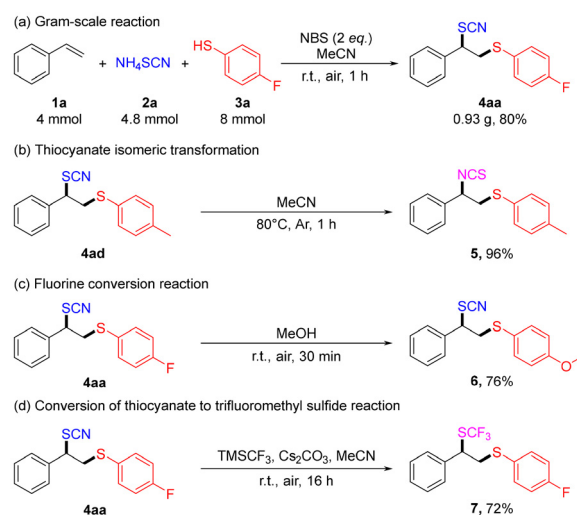
Subsequently, various alkenes were explored (Scheme 3). The styrenes with electron-neutral and electron-donating groups (**1a**, **1g–1i**) provided the corresponding β-thiocyanate sulfides (**4aa**, **4ga–4ia**) in 82–84% yields. However, the presence of an electron-withdrawing group somewhat negatively affected the generation of the desired products (**4ba–4fa**, **4ja–4ka**), with 67–84% yields. Among them, a steric effect of styrene derivatives was not apparent, with the *ortho*-, *meta*-, or *para*-chloro substituents affording the desired products (**4ca**, **4ea**, **4fa**) in 75–82% yields. It is worth noting that fused aryl alkenes smoothly converted to the corresponding products **4la** (65%) and **4ma** (62%). The internal alkene was also attempted, providing the β-thiocyanate sulfide **4na** in 62% yield, which was further identified as a single diastereomeric configuration *via* the ^1H NMR coupling constant and previous reports.^{13a,15} Encouraged by the above results, a series of unactivated aliphatic alkenes were investigated. We were delighted to find that allylbenzene and vinylcyclohexane were compatible with the reaction and gave the corresponding products **4oa** and **4pa**, respectively, in moderate yields. Furthermore, the less reactive cyclic alkenes, such as cyclopentene and cyclohexene, also proceeded smoothly, producing the diastereomeric products **4qa** and **4ra** with 55% and 62% yields, respectively. However, α-methylstyrene was not suitable in this protocol due to the steric hindrance effect; only a trace of **4sa** was detected.

To demonstrate the scalability and practicality of this NBS-promoted thiocyanatothiolsation protocol. A gram-scale reaction of styrene with 4-fluorothiophenol was carried out, and

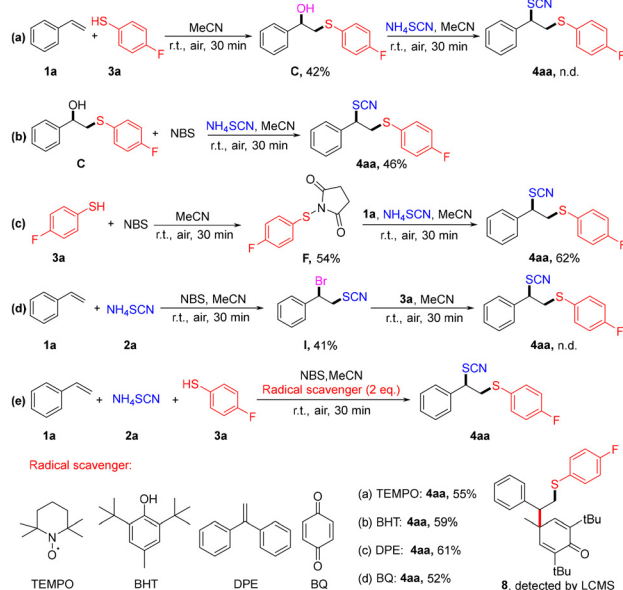
0.93 g of the desired product **4aa** was isolated with 80% yield (Scheme 4a). In addition, it is worth noting that the β-isothiocyanate sulfide **5** was almost quantitatively yielded from **4ad** under heating at 80 °C (Scheme 4b). Subsequently, the **4aa** could be further modification, transformed to **6**, **7** with 76% and 72% yields respectively (Scheme 4c and d). These results demonstrated the synthetic utility of this thiocyanatothiolsation method.

To investigate the potential mechanism, a series of control experiments were carried out (Scheme 5). Initially, in the absence of NBS and **2a**, β-hydroxythiolation compound **C** was obtained in 42% yield. Then, **2a** was added, and no target product **4aa** was yielded (Scheme 5a). However, with the simultaneous addition of **2a** and NBS to **C**, **4aa** was obtained in 46% yield (Scheme 5b). This indicated the crucial role of NBS in this pathway with compound **C** possibly serving as an intermediate. Furthermore, the reaction of **3a** with NBS in the absence of **1a** generated *N*-arylthiosuccinimide **F**, which could be converted to the desired compound **4aa** in 62% yield. This suggested that *N*-arylthiosuccinimide **F** may be an intermediate in this protocol. It is important to note that β-bromothiocyano compound **I** was produced with a 41% yield in the absence of **3a**. Further reaction of compound **I** with **3a**, but no target product was generated. It revealed that compound **I** should be a by-product in the reaction (Scheme 5d). Moreover, when radical scavengers were added to the standard reaction, the reaction was suppressed by about half, and the benzylic radical-captured complex **8** was detected by LC-MS, indicating that a radical pathway should be involved in the system (Scheme 5e).

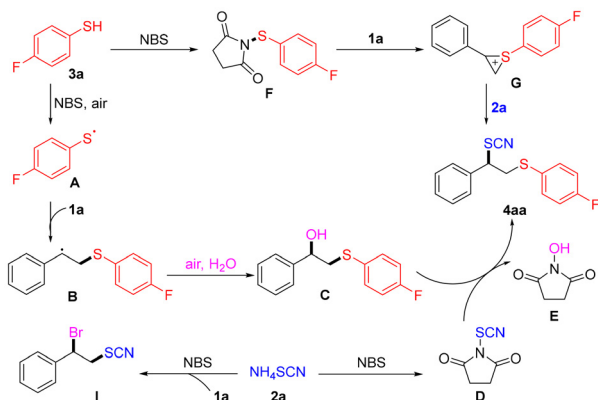
On the basis of the controls and the previous reports,^{10d,g,15} a possible mechanism for this NBS-promoted regioselective thiocyanatothiolsation is proposed as follows (Scheme 6). First, **3a** was oxidized by NBS and air to afford the sulfur radical **A**, which then underwent a radical Michael addition with styrene **1a** to form intermediate **B**. Subsequently, **B** reacted with oxygen and water to engage in a thiol-oxidation-coupling



Scheme 4 Synthetic application experiments.



Scheme 5 Mechanistic investigations. Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), **2a** (0.24 mmol, 1.2 eq.), **3a** (0.4 mmol, 2.0 eq.), NBS (0.4 mmol, 2.0 eq.), MeCN (4.0 mL), under air, room temperature.



Scheme 6 Proposed mechanistic pathway.

(TOCO) reaction, leading to the formation of the styrene β -hydroxythiocyanation compound **C**. Further reaction of intermediate **C** with **2a** and NBS resulted in the desired product **4aa**. Meanwhile, **3a** and NBS could generate the *N*-arylthiosuccinimide **F**, which subsequently reacted with styrene **1a** to form the sulfonium **G**. Finally, intermediate **G** was attacked by nucleophilic reagent **2a** to yield the product **4aa**. Throughout this process, **2a** reacted with NBS, giving β -bromothiocyantation compound **I** as a by-product.

Conclusions

An efficient NBS-promoted three-component thiocyanatothiolation of alkenes with free thiols and NH_4SCN was developed.

The protocol exhibits regioselectivity and high compatibility with a range of styrenes and unactivated alkenes. It avoids pre-activation of thiols, and a diverse range of available thiols can be used directly. Moreover, the simple and mild experimental conditions, fast conversion, and gram-scale applicability of this method will make it practical for the synthesis of diverse sulfur-containing molecules.

Experimental

General procedure for the synthesis of **4**

Styrene **1a** (0.2 mmol, 1.0 eq.), ammonium thiocyanate **2a** (0.24 mmol, 1.2 eq.), 4-fluorobenzenethiol **3a** (0.4 mmol, 2.0 eq.), NBS (0.4 mmol, 2.0 eq.), and MeCN (4.0 mL) were added to an oven-dried round bottom flask (25.0 mL) equipped with a stir bar. The reaction mixture was stirred at room temperature for 30 min. After reaction completion, the solvents were removed under vacuum, and the product **4aa** was obtained by silica gel column chromatography.

General procedure for the synthesis of **5**, **6** and **7**

4ad (0.2 mmol, 1.0 eq.) and MeCN (4.0 mL) were placed in an oven-dried round bottom flask (25.0 mL) equipped with a stir bar. The reaction mixture was stirred at 80 °C for 1 h. After completion, the solvents were removed under vacuum and the product **5** was obtained by silica gel column chromatography. **4aa** (0.2 mmol, 1.0 eq.) and MeOH (4.0 mL) were added to an oven-dried round bottom flask (25.0 mL) equipped with a stir bar. The reaction mixture was stirred at room temperature for 30 min. After reaction completion, the solvents were removed under vacuum and the product **6** was obtained by silica gel column chromatography. Cs_2CO_3 (0.3 mmol, 1.5 eq.) was added to a solution of **4aa** (0.2 mmol, 1 eq.) in CHCN (1.5 mL) and cooled to 0 °C. Then trifluoromethyltrimethylsilane (0.3 mmol, 1.5 eq.) was added at once *via* syringe and the mixture was then stirred at ambient temperature for 16 h. After reaction completion, the solvent was removed under vacuum and the product **7** was obtained by silica gel column chromatography.

General procedure for the gram-scale experiment

Styrene **1a** (4 mmol, 1.0 eq.), ammonium thiocyanate **2a** (4.8 mmol, 1.2 eq.), 4-fluorobenzenethiol **3a** (8 mmol, 2.0 eq.), and NBS (8 mmol, 2.0 eq.), MeCN (20.0 mL) were added to an oven-dried round bottom flask (50.0 mL) equipped with a stir bar. The reaction mixture was stirred at room temperature for 1 h. After reaction completion, the reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over NaCl and concentrated under reduced pressure. The crude product was purified using a silica gel column to obtain the product **4aa** (0.93 g, 80%).

Data availability

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

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Natural Science Foundation of Sichuan (No. 24NSFSC0407) and Fundamental Research Funds for the Central Universities (No. 2682023ZTPY077). We thank the Analysis and Testing Center of Southwest Jiaotong University for structural identification.

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