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NaI-Mediated Acetamidosulphenylation of Alkenes with Nitriles as the Nucleophiles: A Direct Access to Acetamidosulfides

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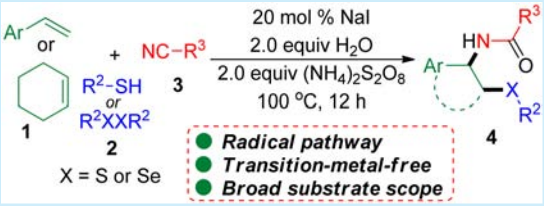
Supporting Information

ABSTRACT: An example of a transition-metal-free, direct, and efficient acetamidosulphenylation reaction of alkenes using nitriles as the nucleophiles via a radical process is presented. This reaction shows a broad substrate scope and high regioselectivity and provides straightforward access to acetamidosulfide derivatives in moderate to high yields.



Acetamidosulfide derivatives are useful chemical entities, which can be converted to many useful compounds.[1] These unique motifs are also present in many natural products,[2] and most of them show various bioactivities and are extensively applied in pharmacology.[3] Compound **A**, which was isolated by Fahey's group from *M. smegmatis*,[2a] performed an important role in the detoxification of alkylating agents and antibiotics;[2b,c] compound **B** showed the inhibition of phospholipase **A2** activity in vitro;[3a,b] and compound **C**, which was isolated from heterologous PKS-NRPS experiments, worked as a useful intermediate for the synthesis of the fungal polyketide synthase (PKS) products (Figure 1).[1]

1,2-Difunctionalization of alkenes has been proven to be a useful strategy in organic synthetic chemistry.[4] Among these reported transformations, the sulphenylation of alkenes for the synthesis of β-functionalized sulfides have drawn much attention.[5−8] In this context, the reaction goes through the thiiranium intermediate formation and ring-opening addition with various nucleophiles to give the 1,2-difunctionalized products (Scheme 1, eq 1).[5−7] In contrast to the other heteroatom nucleophiles, including O,[5] S,[6] and others,[7] examples of using N-based nucleophiles is rare,[8] and a breakthrough in this field was reported by Denmark with azide as a nucleophile and produced the 1,2-difunctionalized products with high selectivity.[8a] Although there are a few other examples using acetonitrile instead of azide as the nucleophile,[8b−d] all these reactions are mediated by a stoichiometric amount of transition metal or strong acid within a handful of substrates (Scheme 1, eq 2). In this context, we wish to report

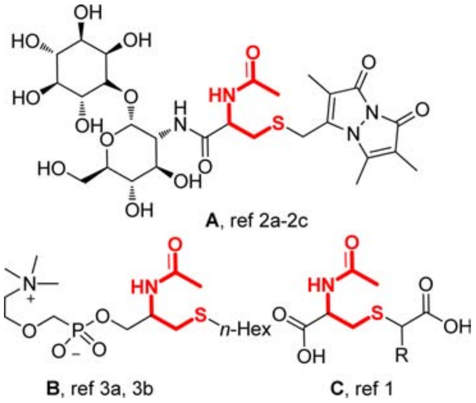
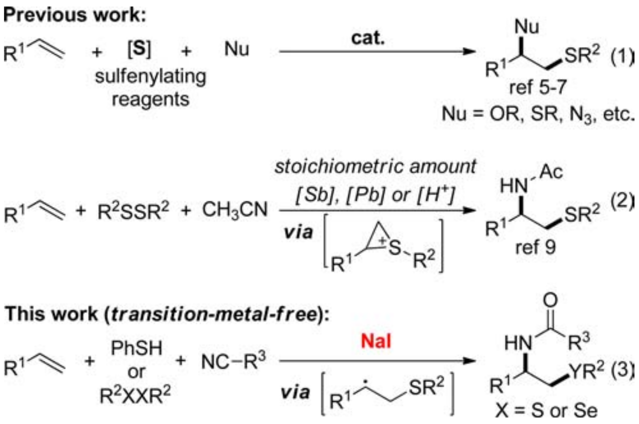


Figure 1. Selected examples of acetamidosulfides.

Scheme 1. Sulphenylation of Alkenes with β-Site Functionalization



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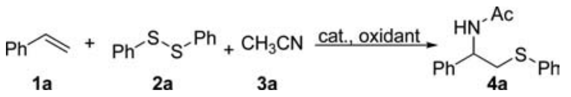
our recent results on direct catalytic acetamidosulphenylation of alkenes with nitriles as nucleophiles under transition-metal-free conditions (Scheme 1, eq 3). Further study shows that the reaction goes through a radical pathway,[9] which is different from the previous mechanism via a cationic intermediate.

Initially, the acetamidosulphenylation reaction of styrene (**1a**) with phenyl disulfide (**2a**) and acetonitrile (**3a**) was catalyzed by TBAI with ammonium persulfate as the oxidant. To our delight, the desired product **4a** was obtained in 48% yield (Table 1, entry 1). It should be noted that the amount of phenyl disulfide (**2a**, 0.15 mmol) was used as the limiting reagent and the yield of **4a** was based on a 0.3 mmol scale. The reaction did not occur in the absence of either catalyst or oxidant (entries 2 and 3). Subsequently, the other catalysts were investigated (entries 4–8), and sodium iodide was proven to be the best (entry 7). In order to enhance the conversion of this reaction, several oxidants were tested, and only inferior results were observed (entries 9 and 10; see Table S1 for details). Further optimization of the reaction temperature enhanced the yield of **4a** to 88% at 100 °C (entries 11 and 12). The best result was obtained in the presence of 2.0 equiv of H_2O with **4a** in 92% isolated yield (entry 13).[8b,c] In addition, when thiophenol instead of phenyl disulfide was used, a comparable yield was obtained (entry 13, result in parentheses).

Table 1. Optimization of Reaction Conditions for Acetamidosulphenylation[a]

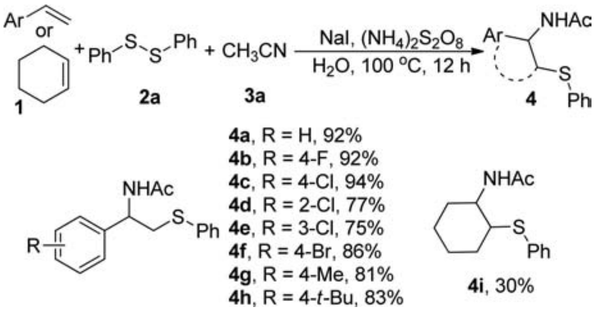


entry	cat.	oxidant	temp (°C)	yield (%)[b]
1	TBAI	$(NH_4)_2S_2O_8$	80	48
2	–	$(NH_4)_2S_2O_8$	80	NR
3	TBAI	–	80	NR
4	TBAC	$(NH_4)_2S_2O_8$	80	trace
5	TBAB	$(NH_4)_2S_2O_8$	80	trace
6	TMAI	$(NH_4)_2S_2O_8$	80	46
7	NaI	$(NH_4)_2S_2O_8$	80	61
8	I_2	$(NH_4)_2S_2O_8$	80	55
9	NaI	$PhI(OAc)_2$	80	NR
10	NaI	TBHP	80	NR
11	NaI	$(NH_4)_2S_2O_8$	90	76
12	NaI	$(NH_4)_2S_2O_8$	100	88
13[c]	**NaI**	**$(NH_4)_2S_2O_8$**	**100**	**92 (89)**[d]

[a] Reaction conditions: Styrene (**1a**, 0.6 mmol), diphenyl disulfide (**2a**, 0.15 mmol), acetonitrile (**3a**, 2.0 mL), catalyst (0.06 mmol), and oxidant (0.6 mmol) at indicated temperature for 12 h. [b] Isolated yield based on 0.3 mmol scale. [c] H_2O (0.6 mmol, 11 μL) was added. [d] Thiophenol (0.3 mmol) instead of phenyl disulfide was used. TBAI = Tetrabutyl ammonium iodide, TBAC = Tetrabutyl ammonium chloride, TBAB = Tetrabutyl ammonium bromide, TMAI = tetramethylammonium iodide.

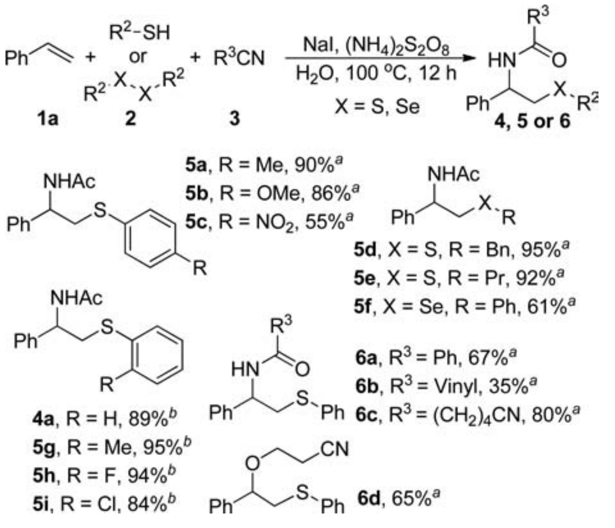
With the optimized results in hand, we have applied this new protocol to various alkenes and the results are illustrated in Scheme 2. All of the tested alkenes performed well and gave the desired products **4** in moderate to excellent yields. When styrenes with *para*-substitutions were used, the corresponding acetamidosulfides were obtained in excellent yields (**4b**, **4c**, and **4f–4h**), while styrenes with substituents on the *ortho*- or *meta*-positions were less reactive compared to the *para*-substituted ones (**4d** and **4e**), which might be due to the steric hindrance. An aliphatic alkene also proceeded smoothly with phenyl disulfide and acetonitrile to give the expected products in acceptable yield (**4i**).

Scheme 2. Acetamidosulphenylation of Alkenes with Acetonitrile and Phenyl Disulfide



To further explore the potential of this methodology, a variety of disulfides and nitriles were investigated under the optimized conditions (Scheme 3). Generally, the substrates of disulfide with electron-donating substituent reacted well to afford **5a–5b** in excellent yields, while the one with a strong electron-withdrawing group showed lower activity and gave **5c** in 55% yield. To our delight, aliphatic disulfides were tolerated under these conditions (**5d**, **5e**). In addition, diselenide was also suitable in this methodology to give the corresponding **5f** in 61% yield. Aryl thiols also performed very well compared to the corresponding disulfides and gave the difunctionalized products in 84–95% yields (**4a**, **5g–5i**). The substrates of **3** containing an aromatic ring or a vinyl or dicyano group were all well-tolerated in our system, giving moderate to good yields (**6a–6c**). When 3-hydroxypropionitrile was employed, the corresponding acetamidosulfide was not observed, and β-alkoxy sulfide **6d** was generated in 65% yield, which indicated the preference of hydroxyl group over the cyano group.

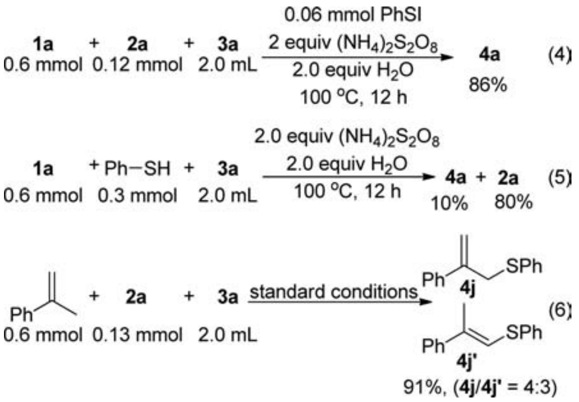
Scheme 3. Acetamidosulphenylation of Styrene with Various Nitriles and Different Disulfides or Thiophenols



[a] Disulfide (**2**, 0.15 mmol) was used as the substrate. [b] Aryl thiol (**2**, 0.3 mmol) was used as the substrate.

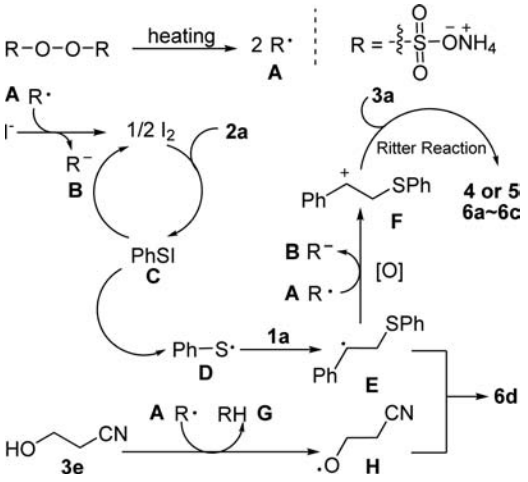
In order to gain insight into the reaction mechanism, several control experiments were performed as shown in Scheme 4.

Scheme 4. Control Experiments



Instead of using sodium iodide as the catalyst, 0.06 mmol of PhSI[10] was introduced to catalyze the reaction and **4a** was obtained in 86% yield, which suggested that intermediate **C** (Scheme 5) might be involved in the transformation (Scheme 4, eq 4). According to the reported literature,[11] the sulfur radical could be generated from thiophenol and then the homocoupling could occur to give disulfide **2a**. Although this step took place quickly, the existing sulfur radical in the system might react with styrene to generate **4a**, and the corresponding control reaction gave **4a** in 10% yield (Scheme 4, eq 5), which indicated that the sulfur radical **D** (Scheme 5) might be involved in this transformation. The generation of vinyl sulfide products **4j** and **4j**′ further confirmed the existence of the radical intermediate **D** in this transformation (Scheme 4, eq 6).[12]

Scheme 5. Proposed Reaction Mechanism



Based on the above-mentioned investigation, a plausible reaction mechanism is proposed in Scheme 5. Initially, the homolytic cleavage of ammonium persulfate gave ammonium sulfate radical anions **A** under thermal conditions.[13] Subsequently, iodide ions were oxidized by **A** to generate iodine and the anion species **B**;[14] a simultaneous process promoted by ammonium persulfate to generate iodine and the anion species **B** is also possible.[15] Then the generated iodine reacted with **2a** to yield PhSI **C**,[10] which would undergo homolytic cleavage to yield the thiophenyl radical **D**.[16] This thiophenyl radical attacked the double bond of alkenes to furnish radical **E**; a similar radical process has been proposed in the oxysulfenylation of alkenes.[12a] The benzylic radical intermediate **E** could be oxidized to a benzylic carbon cation **F**, followed by a Ritter-type reaction to give difunctionalized products.[17] When thiophenol was employed as the material, it likely went through two pathways. First, the thiophenol could be oxidized by ammonium persulfate to generate disulfide;[18] alternatively, the radical **A** captured a hydrogen atom from thiophenol to generate thiophenyl radical **D** and then followed the above-mentioned process.[19] In the case of **3e**, the hydroxyl group may have been attacked by **A** to form another radical **H**. Final radical coupling of **E** and **H** gave **6e**.[12a] Additional control reactions with TEMPO as an additive further confirmed this radical process (see Table S2 for details).

In summary, we have developed an efficient, facile, and direct acetamidosulphenylation reaction of alkenes using nitriles as the nucleophiles catalyzed by sodium iodine with ammonium persulfate as an oxidant. The reaction conditions are mild and suitable for a wide range of substrates, including aryl or alkyl nitriles, disulfides, arylthiols, and even diselenide, and all give the corresponding products in moderate to excellent yields. This transition-metal-free difunctionalization protocol provides a practical one-pot access to a variety of acetamidosulfide derivatives. In addition, a plausible mechanism involving a radical pathway is proposed for this three-component reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02752.

Detailed experimental procedures and characterization data of the products (PDF)

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Notes

The authors declare no competing financial interest.

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