ARTICLE IN PRESS

Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Metal-free three-component synthesis of thioamides from β-nitrostyrenes, amines and elemental sulfur

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ARTICLE INFO

Article history:
Received 10 March 2021
Revised 9 April 2021
Accepted 14 April 2021
Available online xxxx

Keywords:
C=C bond cleavage
Metal-free
Three-component reaction
Thioamides

ABSTRACT

A metal-free C=C bond cleavage reaction of β-nitrostyrenes in the presence of elemental sulfur and secondary amines/amides is described. Elemental sulfur serves as both a raw material and an oxidant for C=C bond cleavage, and secondary amines or amides are both feasible nitrogen sources. Besides mild reaction condition and simple work-up procedure, the method provided thioamides with good to excellent yields.

Introduction

As one of the characteristic molecular fragments containing C=S bond, thioamides are useful intermediates for the synthesis of various compounds, including some heterocycles and ligands [1]. Furthermore, thioamides showed wide applications in medicinal chemistry [2]. So far, many approaches have been developed for the preparation of thioamides. The popular method is direct addition of H_2S or other sulfide surrogates to the cyanide group under pressure condition [3]. Another traditional synthetic method is to convert the carbonyl group to a thiocarbonyl group using Lawesson's reagent and its analogs, but this sulphur phosphorus reagent produces phosphorus waste [4]. Currently, due to its rich resource, eco-friendliness and high atomic utilization, elemental sulfur is often used as an alternative and preferred sulfur reagent to build sulfur-containing compounds [5]. The Willger-Kindler reaction uses arylmethyl ketones, amines and elemental sulfur to synthesize thioamides, with the disadvantage of requiring harsh reaction conditions [6]. Moreover, the coupling reaction of amides and elemental sulfur with alkynes, amines, and aldehydes has been reported to be an effective method for the synthesis of thioamides [7]. In recent years, organic skeletons which are cleaved by C—C bonds to form new C-X bonds have attracted considerable attention in the field of organic synthesis [8], and some methods for constructing thioamides by means of C—C bonds cleavage have been gradually established [9]. Such as decarboxylation/thioamidation of aryl acetic acid and cinnamic acid [9a], decyanation/thioamidation of arylacetonitriles [9b], cleavage of C=C bond of aryl ethylene with elemental sulfur and amide [9c], and cleavage of carbon–carbon triple bond of aryl acetylenes with elemental sulfur and amide [9d]. We recently reported a novel process involving a C—N bond cleavage and C—H bond thionation of α-azido ketones to construct a thioamide functional motif in the presence of elemental sulfur [10], at the same time, the research interests of our group focus on the development of new reactivities of nitroalkenes. [11,13] Herein, we report a base-promoted metal-free C=C bond cleavage reaction of β-nitrostyrenes in the presence of elemental sulfur and secondary amines/amides. This three-component reaction has proven to be a beneficial method for achieving substituted thioamides.

Results and discussion

To commence our study, β-nitrostyrene (**1a**), elemental sulfur and morpholine (**2a**) were chosen as model substrates for the three-component reaction, and the detail are summarized in (Table 1). Firstly, the reaction cannot be carried out without any additives (entry 1). Then some copper(II) salts were introduced

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https://doi.org/10.1016/j.tetlet.2021.153092
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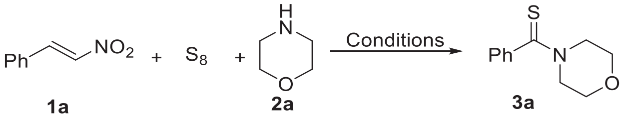
Please cite this article as: L. Peng, L. Ma, Y. Ran et al., Metal-free three-component synthesis of thioamides from β-nitrostyrenes, amines and elemental sulfur, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2021.153092

Table 1
Optimization of reaction conditions.[a]



Entry	Cat.	Base	Temp (°C)	Solvent	Yield (%)[b]
1	–	–	110	DMSO	n.d.
2	Cu(acac)$_2$	–	110	DMSO	n.d.
3	CuBr$_2$	–	110	DMSO	n.d.
4	Cu(OAc)$_2$	–	110	DMSO	n.d.
5	–	K_2CO_3	110	DMSO	60
6	–	Na_2CO_3	110	DMSO	43
7	–	$NaHCO_3$	110	DMSO	48
8	–	Cs_2CO_3	110	DMSO	75
9	–	NaOH	110	DMSO	55
10	–	NaOAc	110	DMSO	63
11	–	*t*-BuOK	110	DMSO	80
12	–	DBU	110	DMSO	72
13	–	Et_3N	110	DMSO	23
14	–	*t*-BuOK	100	DMSO	88
15	–	*t*-BuOK	80	DMSO	31
16	–	*t*-BuOK	100	1,4-Dioxane	77
17	–	*t*-BuOK	100	DMF	trace
18[c]	–	*t*-BuOK	100	DMSO	85

[a] Reaction conditions: 1a (0.13 mmol, 1.0 equiv), 2a (0.39 mmol, 3.0 equiv), catalyst (10 mol %), base (0.26 mmol, 2.0 equiv), Sulfur (0.26 mmol, 2.0 equiv), solvent (0.5 mL), under air, 2 h.

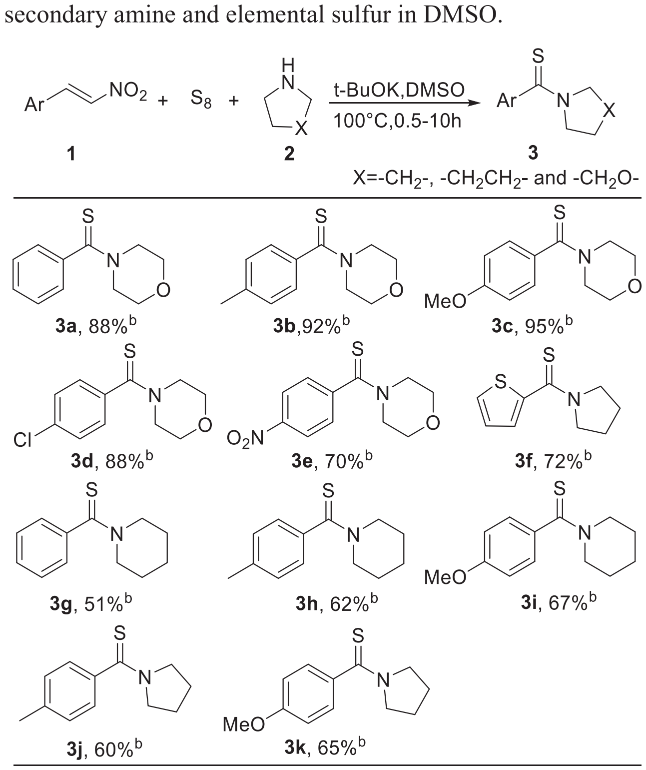
[b] Isolated yields.

[c] Under Ar atmosphere.

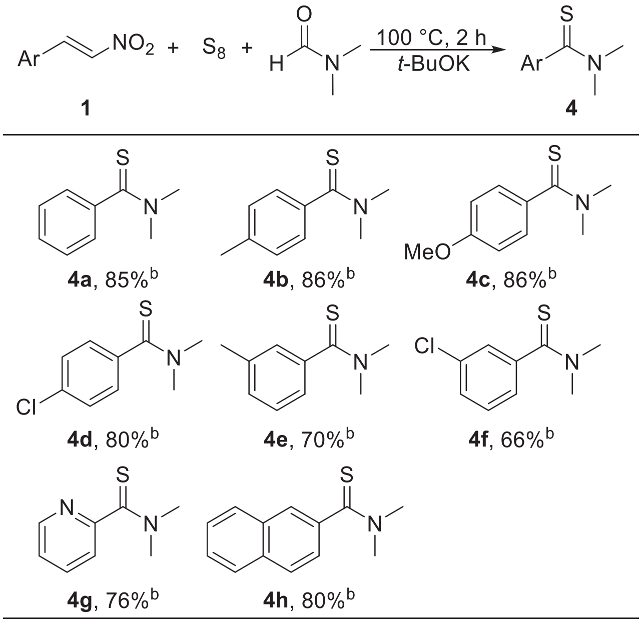
to the reaction, but this attempt was proved to be invalid (entries 2–4). To our delight, when K_2CO_3 was introduced to this reaction, the desired product **3a** (4-morpholinylphenylmethanethione) was obtained in 60% yield (entry 5). Based on this attractive result, a series of different bases, namely Na_2CO_3, $NaHCO_3$, Cs_2CO_3, NaOH, NaOAc and *t*-BuOK were tested. It was found that *t*-BuOK exhibited the best promotion effect on the reaction, producing product **3a** in 80% yield (entries 6–11). The other two organic bases (DBU and Et_3N) were not as effective as *t*-BuOK in this reaction (entries 12 and 13). Further lowering the reaction temperature to 100 °C, the yield of **3a** was increased to 88% (entry 14). When the temperature was continued to lower to 80 °C, the yield of **3a** was dropped to 31% (entry 15). Screening of solvent showed that 1,4-dioxane or DMF were not as effective as DMSO (entries 14, 16 and 17). Surprisingly, when DMF was used as a solvent, the *N*, *N*-dimethylbenzene was obtained in 70% yield as a major product and only trace amount of **3a** was obtained (entry 17). This means that amide could also be used as an amine source. Finally, the reaction was conducted under Ar atmosphere, the yield of the target product could not be improved significantly (entry 18). Thus, the *t*-BuOK/DMSO at 100 °C was chosen as the optimal reaction condition.

Once the optimized reaction conditions were established, the scope of substrates was studied (Scheme 1). Overall, the reaction of morpholine as the amine source could produce the corresponding products in high yields ranging from 70% to 95% (**3a**, **3b**, **3c**, **3d**, **3e**). Amines such as piperidine and pyrrolidine were suitable for this reaction and they could also produce corresponding products in moderate yields ranging from 45% to 65% (**3g, 3h, 3i, 3j, 3k**). The scope of the substrate was extended to the heterocyclic β-nitrostyrene to produce the **3f** with a yield of 72%. Obviously, electron-donating group displayed higher reactivity than the electron-withdrawing group β-nitrostyrene, and the secondary amine with strong basicity was more beneficial to the reaction.

According to the unexpected discovery of Table 1, we found that DMF could be severed as amine source for the formation of thioamides. When nitroolefins and sulfur was stirring in DMF in the presence of *t*-BuOK, the corresponding thioamides could be acquired with moderate to high yield (Scheme 2). It was found that nitroolefins with electron-donating group (**4b**, **4c**) gave a higher yield than electron-withdrawing group (**4d**). Further studies were



Scheme 1. Reactions of different β-nitrostyrenes with secondary amine and elemental sulfur in DMSO.

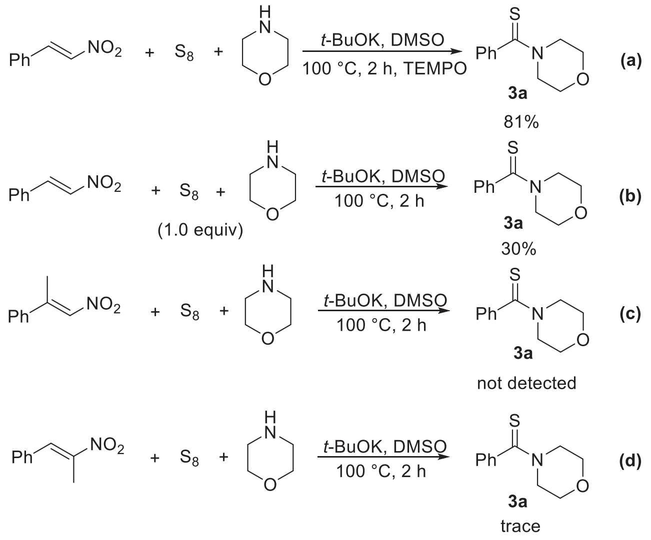


Scheme 2. Reactions of different α-nitrostyrenes with DMF and elemental sulfur.

devoted towards the *meta*-substituted β-nitrostyrene gave the corresponding products in 70% and 66% yields respectively (**4e**, **4f**). Finally, β-nitrostyrene with aromatic heterocycle also yielded corresponding products in considerable yields (**4g**, **4h**), which further expanded the scope of the reaction.

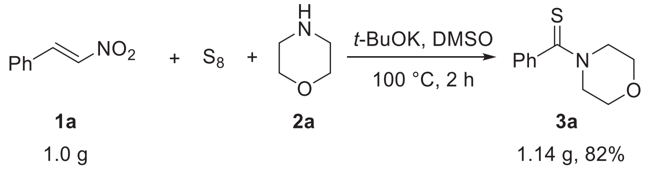
In order to explore the practicability of this reaction, 1 g of **1a** was reacted under the optimum conditions for 2 h. As a result, 1.14 g of **3a** was obtained, and the yield was up to 82%. It showed that the method had strong practicability in preparing thioamides (Scheme 3).

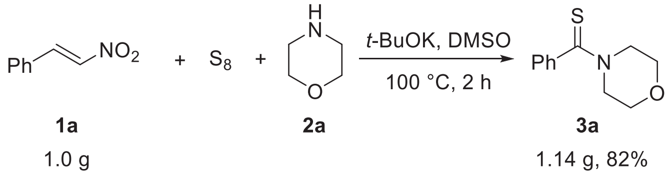
To further understand this three-component reaction in depth and explored the reaction process, some control experiments were carried out (Scheme 4). Firstly, the reaction gave satisfied yield in the presence of radical inhibitor TEMPO, which revealed that this reaction might not involve a radical process. Secondly, it was found that the equivalent of elemental sulfur was crucial to this reaction, one equivalent of elemental sulfur cannot give full conversion of nitroolefin. Moreover, the β-disubstituted nitrostyrene did not produce the corresponding product, which indicated that the reaction process involved a C=C bond cleavage (Scheme 4c). While isomeric α-methyl-β-nitrostyrene exhibited poor reactivity and only gave trace product (Scheme 4d).



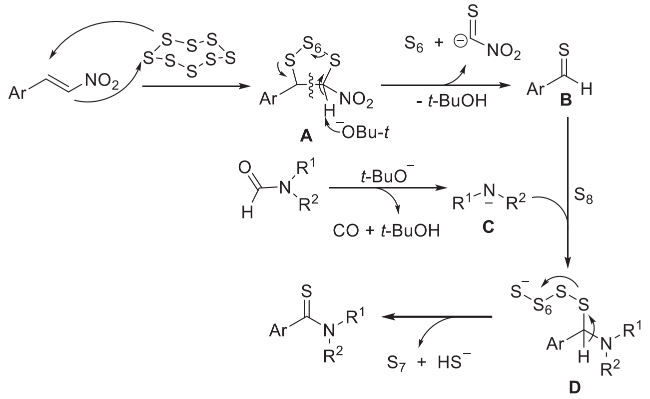
Scheme 4. Control experiments.

Based on these observations, a possible mechanism is proposed in Scheme 5. **9a** First, β-nitrostyrene was reacted with S_8 to form the cyclization product **A**. Then, the proton on the ring of **A** was captured by *t*-BuOK to drive the C—C bond cleavage to form the thioaldehyde **B**, accompany with nitrothioformaldehyde and S_6. At the same time, the secondary amine was deprotonated with the aid of alkali to form the amino anion **C**. During this process, if the amine source is DMF, the carbonyl group will be removed as CO [11,12]. Subsequently, the intermediate **B** suffered oxidation by S_8 was nucleophilic attacked by the amino anion **C** to yield the intermediate **D**. Finally, the desired product was obtained by the elimination of sulfhydryl ion.





Scheme 3. Large-scale synthesis.



Scheme 5. Possible mechanism.

Conclusions

In summary, we have developed a novel method to synthesize thioamides through a three-component reaction based on the metal-free C═C bond cleavage method, by using β-nitroolefins as raw materials, secondary amines/amides as the amine source. The elemental sulfur serves as both a raw material and an oxidant for C═C bond cleavage. This method has a wide range of substrates, strong applicability, and good isolated yield.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (31601675), the PhD Start-up Fund of Hubei University of Science and Technology (BK201821), the High-level Talents Project of Xianning City (2019) and the Graduate Innovative Fund of Wuhan Institute of Technology.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153092.

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