Tetrahedron Letters 75 (2021) 153202

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Metal-free chalcogenation of cycloketone oxime esters with dichalcogenides

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ARTICLE INFO

Article history:
Received 29 March 2021
Revised 15 May 2021
Accepted 20 May 2021
Available online 24 May 2021

Keywords:
Chalcogenation
Cycloketone oxime esters
Dichalcogenides
Metal-free protocols

ABSTRACT

We report the metal-free chalcogenation of cycloketone oxime esters with dichalcogenides via a radical process. Because of the metal-free condition and use of readily accessible dichalcogenides, this method is an effective and green strategy for the synthesis of chalcogen-substituted butyronitrile.

Introduction

Organochalcogen compounds have received continuous attention because of their extensive applications as pharmaceuticals, drug candidates, agrochemicals, catalysis and functional materials [1]. Some representative examples are shown in Fig. 1. Axtinib is an anti-cancer drug [2]. Amenamevir is an anti-infective drug [3]. Compound **1** is a human breast cancer cell growth inhibitor [4]. Compound **2** is a retinoic acid receptor agonist [5]. Compound **3** is a fluorescence probe [6]. Hence, the formation of carbon-chalcogen bonds in an efficient manner is highly desirable.

In the past decade, cyclobutanone oxime esters have emerged as versatile intermediates in organic synthesis as they can be converted to functionalised nitriles via iminyl radicals. This type of transformation involves the formation of new C—C, C—O, C—N, and C–X bonds and is realised by transition-metal catalysis [7], acid catalysis [8], microwave irradiation [9], photocatalysis [10] and Lewis base activation [11]. However, carbon–chalcogen bond formation *via* fragmentation of cycloketone oxime esters has not been widely studied (Scheme 1). In 2005, Nishimura and Uemura reported Ir-catalysed ring cleavage of cycloketone oxime esters with diphenyl dichalcogenides to synthesize three phenyl alkyl chalcogenides [12]. In 2019, Zhou and coworkers reported a photocatalytic sp^3 C—S and C–Se bond formation through C—C bond cleavage of cycloketone oxime esters [13]. Wang and Ji reported a nickel-catalysed thiolation/ and selenylation of cycloketone oxime esters with thiosulfonate or selenium sulfonate [14]. Recently, we reported an ethanol/*N*,*N*-dimethylacetamide promoted sp^3 C-SCF$_3$ coupling reaction between cycloketone oxime esters and *S*-trifluoromethyl 4-methylbenzenesulfonothioate [15]. As a part of our on-going research to develop efficient methods for carbon-chalcogen bond formation [16], we demonstrate herein metal-free chalcogenation of cycloketone oxime esters with dichalcogenides to form sp^3 carbon chalcogen-bonds.

Results and discussion

Cyclobutanone O-(4-(trifluoromethyl)benzoyl) oxime (**4a**) was treated with 1,2-di-p-tolyldisulfane (**5a**) in *N*,*N*-dimethylacetamide (DMA) at 120 °C [15]. Fortunately, the desired thiolation product **6aa** was obtained in 56% yield (Table 1, entry 1). To further improve the yield, first, various solvents such as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1-methyl-2-pyrrolidinone (NMP), toluene, acetonitrile (MeCN), and butyronitrile (PrCN) (Table 1, entries 2–7) were investigated, among which PrCN afforded the highest yield. Next, the reaction temperature was investigated. When the reaction temperature was decreased to 100 °C, no reaction took place. However, when the reaction temperature was increased to 140 °C, the yield improved to 75% (entries 8 and 9). Finally, the reaction concentration and the leaving groups were studied. When the concentration of 4a was increased from 0.1 to 0.2 M, the yield increased from 75% to 77% (entry 10).

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https://doi.org/10.1016/j.tetlet.2021.153202
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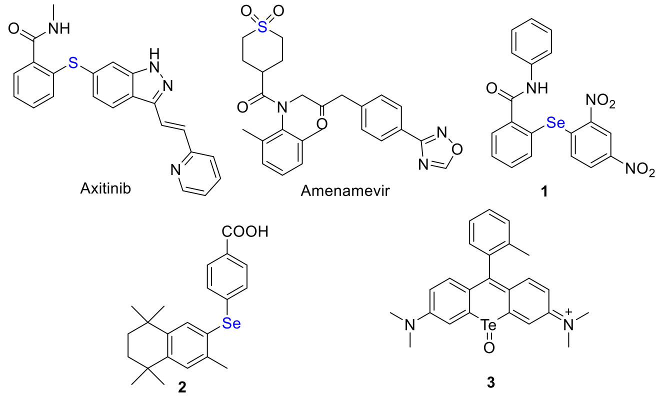
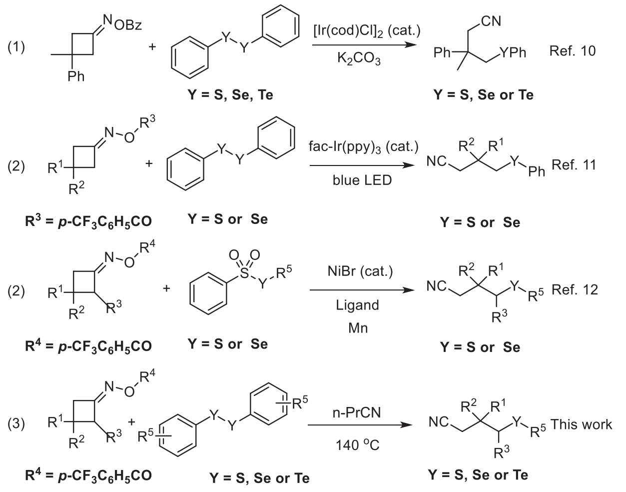


Fig. 1. Representative organochalcogen compounds with diverse functions.



Scheme 1. Carbon-chalcogen bonds formation *via* fragmentation of cycloketone oxime esters.

However, further increasing the reaction concentration decreased the yield (entry 11). Notably, when 3, 5-(ditrifluoromethyl)benzoic ester and perfluorobenzoic ester instead of 4-(trifluoromethyl)benzoic ester was employed, trace product and 72% yield of the product was obtained respectively. Thus, the optimised reaction conditions for thiolation of 4a were as follows: **4a** (0.30 mmol), **5a** (0.36 mmol), and PrCN (1.5 mL) at 140 °C.

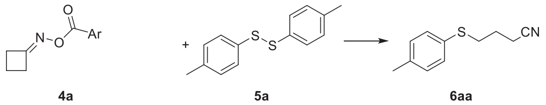
With the optimised reaction conditions in hand, the reaction scope was investigated with various disulfides and **4a**; the results are presented in Scheme 2. Phenyl disulfide bearing electron-donating or electron-withdrawing substituents in para-, meta-, or ortho-positions were well tolerated and afforded the desired products (**6ab**–**6ak**). Moreover, 1,2-di(naphthalen-2-yl)disulfane (**5 l**) and 1,2-di(thiophen-2-yl)disulfane (**5 m**) could afford the respective products **6al** and **6am** in good yields.

Next, a series of cycloketone oxime esters and aryl disulfides were tested under the optimised conditions. The results are summarised in Scheme 3. 3-Phenyl cyclobutanone oxime ester (**4b**) and 3-aryl cyclobutanone oxime esters with *para*- or *meta*-substitution on the phenyl ring (**4c**–**4f**) were compatible with this transformation and furnished the desired products (**6ba**–**6fa**). In addition, 3-ethoxycarbonyl-, 3-((*tert*-butoxycarbonyl)amino)-, 3-benzyloxy-, and 3-methyl-3-phenyl-substituted cyclobutanone oxime esters (**4g**–**4j**) as well as Boc-protected 7-azaspiro[3.5] nonan-2-one oxime ester (**4k**), Boc-protected azetidin-3-one oxime ester (**4l**), and oxetan-3-one oxime ester (**4m**) were treated with **5a** and were found to afford the desired products (**6ga**–**6ma**) in moderate to good yields. Notably, when 2-benzyl-substituted cyclobutanone oxime was used, its perfluorobenzoic ester instead of 4-(trifluoromethyl)benzoic ester was employed, which afforded the desired product (**6na**) in 41% yield. Moreover, other functionalised nitriles (**6bh**–**6lh**) could be prepared from the corresponding cycloketone oxime esters and aryl disulfides under the optimised reaction conditions. However, when cyclopentanone O-(4-(trifluoromethyl)benzoyl) oxime was employed as substrate, the desired product **6oa** was obtained in low yield.

To further broaden the substrate scope of this reaction, cycloketone oxime esters (**4a**, **4b**, **4c**, **4e**, **4h**, **4i**, **4k**, and **4m**) were coupled with aryl diselenides (**7a**–**7f**) and phenyl ditelluride (**7g**). The results are shown in Scheme 4. In all cases, the desired phenyl alkyl selenides (**8aa**–**8af**) and phenyl alkyl tellurides (**8ag**–**8eg**) were obtained in moderate to good yields.

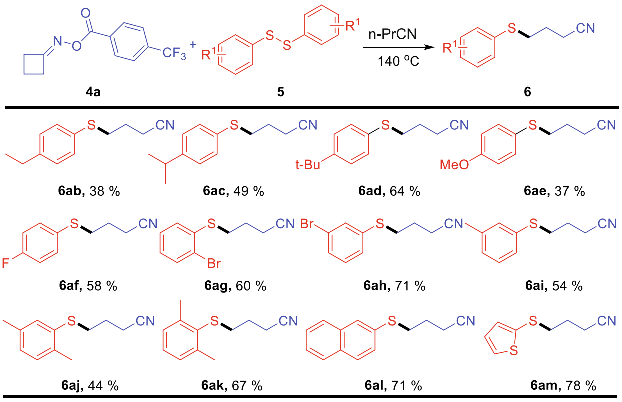
A plausible mechanism for chalcogenation is proposed on the basis of the aforementioned results and related literature [9] (Scheme 5). Initially, pyrolysis of cyclobutanone oxime esters **4a**

Table 1
Reaction Optimization[a].



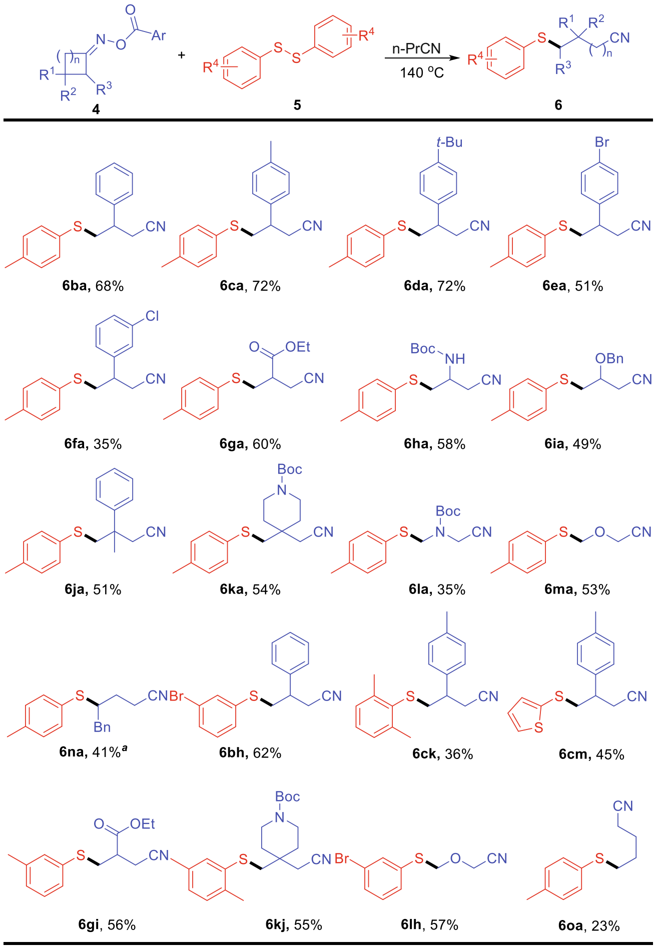
Entry	Solvent (mL)	Temperature (°C)	Reaction time (h)	Yield (%)
1	DMA (3.0 mL)	120	12	56
2	DMF (3.0 mL)	120	12	39
3	DMSO (3.0 mL)	120	12	trace
4	NMP (3.0 mL)	120	12	trace
5	Toluene (3.0 mL))	120	12	trace
6	MeCN (3.0 mL)	120	12	58
7	PrCN (3.0 mL)	120	12	72
8	PrCN (3.0 mL)	100	19	N.R.
9	PrCN (3.0 mL)	140	19	75
10	n-PrCN (1.5 mL)	140	19	77
11	PrCN (0.5 mL)	140	19	68
12	PrCN (0.5 mL)	140	19	trace[b]
13	PrCN (0.5 mL)	140	19	72[c]

[a] Reaction conditions: **4a** (0.30 mmol), **5a** (0.36 mmol) in solvent (0.5–3.0 mL) at indicated temperature for 12–19 h, Ar = 4-(trifluoromethyl)phenyl.
[b] Ar = 3, 5-(di trifluoromethyl)phenyl.
[c] Ar = perfluorophenyl.



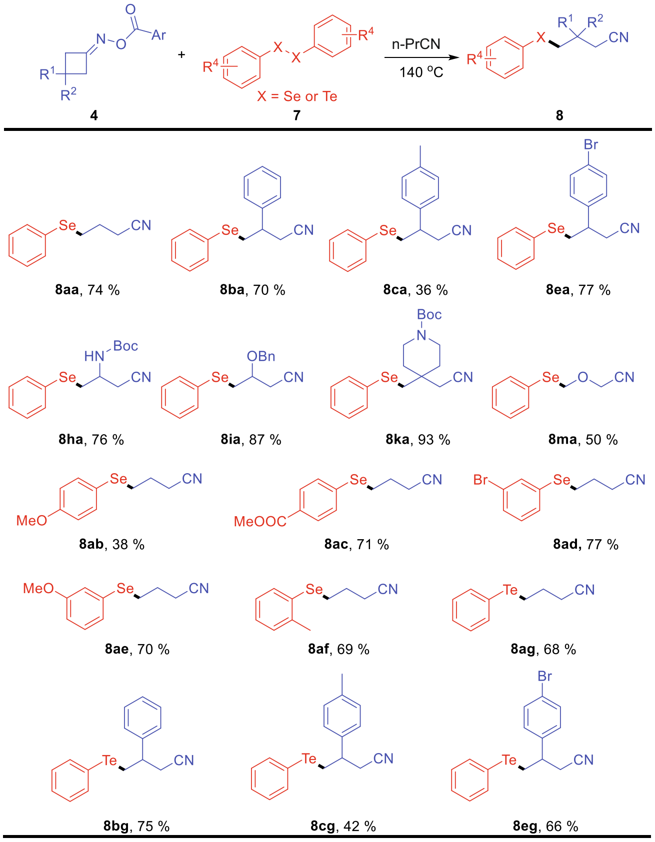
Reaction conditions: **4a** (0.30 mmol), **5** (0.36 mmol in n-PrCN (1.5 mL), at 140 °C for 12-19 h,

Scheme 2. Substrate Scope for thiolation of 4a.



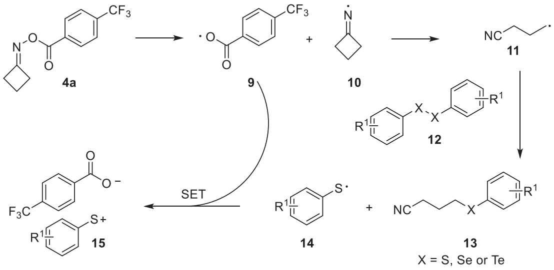
Reaction conditions: **4** (0.30 mmol), **5** (0.36 mmol in n-PrCN (1.5 mL), at 140 °C for 12-19 h, Ar = 4-(trifluoromethyl)phenyl. [a] Ar = perfluorophenyl.

Scheme 3. Scope for thiolation of cyclobutanone oxime esters.

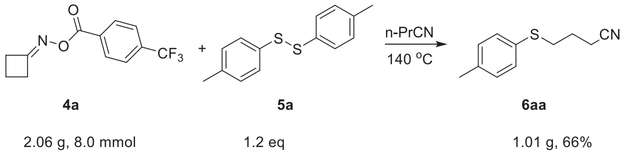


Reaction conditions: **4** (0.30 mmol), **7** (0.36 mmol in n-PrCN (1.5 mL), at 140 °C for 12-19 h, Ar = 4-(trifluoromethyl)phenyl.

Scheme 4. Scope for chalcogenation of cyclobutanone oxime esters.



Scheme 5. Plausible mechanism for chalcogenation of cyclobutanone oxime esters.



Scheme 6. Scale up of the thiolation reaction.

leads to the generation of 4-(trifluoromethyl)benzoate radical **9** and iminyl radical **10**, which is converted to cyanoalkyl radical **11** via a ring-opening process. Intermediate **11** reacts with dichalcogenide **12** to afford the chalcogenation product (**13**) and sulfur radical (**14**). Finally, single electron transfer between **14** and **8** affords salt **15**.

Finally, to illustrate the possible practical application of this transformation, a gram-scale thiolation of **4a** was conducted (Scheme 6). To our delight, the desired product **6aa** was obtained in 66% yield.

Conclusion

We conducted the metal-free chalcogenation of cycloketone oxime esters with dichalcogenides via a radical process for the first time. The metal-free condition and the readily accessible dichalcogenides make this method an alternative and green strategy for the synthesis of chalcogen-substituted alkyl nitriles. The synthesis of other chalcogen-substituted allyl nitriles from cycloketone oxime esters by this strategy is underway in our laboratory, and the results will be reported in due time.

Declaration of Competing Interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

Acknowledgements

The authors sincerely thank the financial support from National Natural Science Foundation of China (Grant 22077095) and Natural Science Foundation of Tianjin City (Grant 18JCQNJC76600).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153202.

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