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Synthesis of 3-acyl-5,6-dihydro-1,4-oxathiines through ring expansion of thiiranes

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ABSTRACT

Synthesis of 3-acyl-5,6-dihydro-1,4-oxathiines has been achieved via reactions of thiiranes and α-diazo-β-1,3-dicarbonyl compounds under microwave and copper sulfate-assisted conditions. The current method provides a direct and simple strategy in efficient preparation of 3-acyl-1,4-oxathiines from readily available thiiranes and *trans*-3-acyl-5,6-dihydro-1,4-oxathiines as stereospecific products for 1,2-disubstituted *cis*-thiiranes. The reaction mechanism was also proposed.

Introduction

Chemistry of 1,4-oxathiine derivatives has attracted more and more attention by agrochemists and medicinal chemists since 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxanilide (Vitavax) was discovered as an well-established systemic fungicide for preventing and controlling cereal smut and wheat rust in 1966 (Fig. 1).[1] A great deal of synthetic work has been done aimed at creating various analogues of Vitavax derivatives, some of which have also become commercial fungicides.[2] Later, oxathiine carboxanilide (OC), one of 1,4-oxathiine-3-carboxamide derivatives, had been found as a very highly active anti-HIV agent in screening anti-AIDS drugs.[3] Subsequently, the relationship between the structure and activity of oxathiine carboxanilides and their derivatives has been studied and the results indicated that 5,6-dihydro-1,4-oxathiine-3-carboxamide is the most important structural unit that determined OC drug activity.[4,5] In addition, 3-acyl-5,6-dihydro-1,4-oxathiines are also very important organic synthetic intermediates, which can further occur other reactions, such as ring opening,[6] oxidation,[7,8] and reduction.[9,10]

Although 3-acyl-5,6-dihydro-1,4-oxathiines have been widely applied in organic synthesis and medicinal chemistry, their synthetic methods are very limited to date. There are three common methods for their preparation: a) substitution of ethyl 2-chloro-3-oxobutanoate with 2-mercaptoethanol and subsequent cyclization[4,5,11]; this is a general method for the preparation of Vitavax; b) cyclization of (*E*/*Z*)-2-chloro-2-(2-hydroxyethylthio)butenamides under the action of LiHMDS in low yields[12]; c) hetero-Diels-Alder cycloadditions of 2,4-dioxopentane-3-thione as electron-deficient heterodiene and electron-rich enolic ethers in long reaction time (Scheme 1).[13] In view of the importance of 3-acyl-5,6-dihydro-1,4-oxathiines and drawbacks of the existing synthetic methods, the development of alternative general methods to synthesize these compounds is in high demand.

In 2014, Lacour and coworkers realized synthesis of 2-acyl-1,4-dioxene derivatives through reactions of epoxides and α-diazo-β-dicarbonyl compounds under the catalysis of a combination of [CpRu(CH_3CN)$_3$][BArF] and 1,10-phenanthroline (Scheme 2).[14] Thiiranes have unique chemical properties and have been of interest in our laboratory in recent years.[15,16] They are readily available from oxiranes. We, herein, present a new synthetic strategy for the

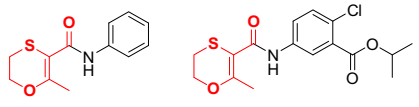

Fig. 1. Structures of Vitavax and oxathiine carboxanilides.

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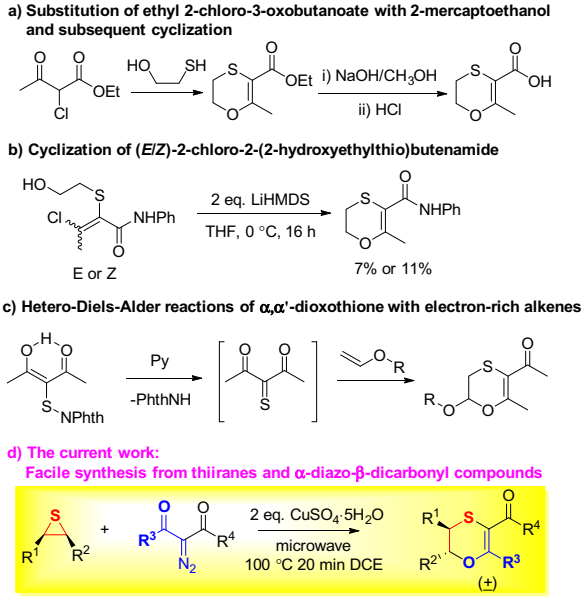
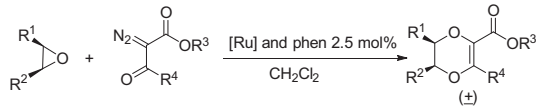


Scheme 1. Synthesis of 3-acyl-5,6-dihydro-1,4-oxathiines.



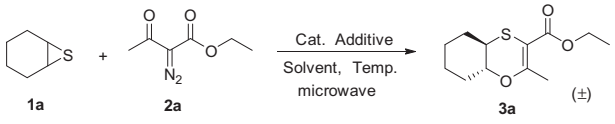
Scheme 2. Synthesis of 5,6-dihydro-1,4-dioxenes.

preparation of 3-acyl-5,6-dihydro-1,4-oxathiines through reactions of thiiranes and α-diazo-β-dicarbonyl compounds under microwave and copper sulfate-assisted conditions (Scheme 1).

Results and discussions

At the outset of this study, 7-thiabicyclo[4.1.0]heptane (**1a**) and ethyl 2-diazo-3-oxobutanoate (**2a**) were employed as the model substrates to optimize reaction conditions (Table 1). Initially, we screened catalysts and found that $Cu(hfacac)_2{\cdot}xH_2O$, Rh, Pd, and Zn salt catalysts were unable to get the corresponding product **3a** (Table 1, entries 1–4). Other mild catalysts such as various silver catalysts and a series of Lewis acid catalysts such as $BF_3{\cdot}OEt$, $FeCl_3$, and $AlCl_3$ were attempted. Unfortunately, no desired product **3a** was observed (Not shown in Table 1). When catalyst $(CF_3SO_3)_2Cu$ was used, only a trace amount of product **3a** was obtained (Table 1, entry 5). However, product **3a** was obtained in 36% yield when equivalent amount of $CuSO_4{\cdot}5H_2O$ was used as the catalyst (Table 1, entry 6). We further optimized the reactant ratio and found that a good yield was obtained when the ratio of **1a**:**2a** was increased to 2:1 (Table 1, entry 7). When the reaction time was reduced from 40 mins to 20 mins, the yield was slightly improved (Table 1, entry 9). Next, we carried out experiments at different reaction temperatures and found that when the temperature was increased to 120 °C, the yield dropped sharply, the reaction system became very complex. However, when the temperature was lowered to 80 °C, the reaction hardly occurred, revealing that the reaction is sensitive to temperature (Table 1, entries 10 and 11). Further optimization on the amount of the catalyst $CuSO_4{\cdot}5H_2O$ indicates that the best yield of 55% was obtained when 2 equiv. of $CuSO_4{\cdot}5H_2O$ applied. Further increasing the

Table 1
Optimization for the reaction of 7-thiabicyclo[4.1.0]heptane (**1a**) and ethyl 2-diazo-3-oxobutanoate (**2a**).[a]



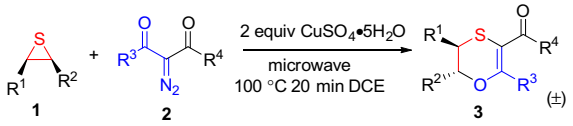
Entry	1a/2a	Cat. (equiv.)	Addttive (equiv.)	Temp. ( )	Time (min.)	Solvent	Yield (%)[b]
1	2/1	$Cu(hfacac)_2{\cdot}xH_2O$ (0.2)		100	20	DCE	0
2	2/1	$Rh_2(OAc)_4$ (0.2)		100	20	DCE	0
3	2/1	$Pd(OAc)_2$ (0.2)		100	20	DCE	0
4	1/1	$Cu(CH_3CN)_4PF_6$ (0.2)		100	40	DCE	0
5	1/1	$(CF_3SO_3)_2Cu$ (1)		100	40	DCE	Trace[d]
6	1/1	$CuSO_4{\cdot}5H_2O$ (1)		100	40	DCE	36
7	2/1	$CuSO_4{\cdot}5H_2O$ (1)		100	40	DCE	40
8	1/1.5	$CuSO_4$ $5H_2O$ (1)		100	40	DCE	37
9	2/1	$CuSO_4{\cdot}5H_2O$ (1)		100	20	DCE	41
10	2/1	$CuSO_4{\cdot}5H_2O$ (1)		120	20	DCE	12
11	2/1	$CuSO_4{\cdot}5H_2O$ (1)		80	20	DCE	0
12	2/1	$CuSO_4{\cdot}5H_2O$ (2)		100	20	DCE	55 (65[c])
13	2/1	$CuSO_4{\cdot}5H_2O$ (3)		100	20	DCE	40
14	2/1	$CuSO_4{\cdot}5H_2O$ (0.5)		100	20	DCE	Trace[d]
15	2/1	$CuSO_4{\cdot}5H_2O$ (2)		100	20	Toluene	15
16	2/1	$CuSO_4{\cdot}5H_2O$ (2)		100	20	MeCN	8
17	2/1	$CuSO_4{\cdot}5H_2O$ (2)		100	20	1,4-dioxane	33
18	2/1	$CuSO_4$ (2)		100	20	DCE	Trace[d]
19	2/1	$CuSO_4$ (2)	H_2O (10)	100	20	DCE	39
20	2/1	$CuSO_4$ (2)	HO OH (4)	100	20	DCE	22
21	2/1	$CuSO_4$ (2)	—O O— (4)	100	20	DCE	0
22	2/1	$CuSO_4$ (2)	H_2N NH_2 (4)	100	20	DCE	0

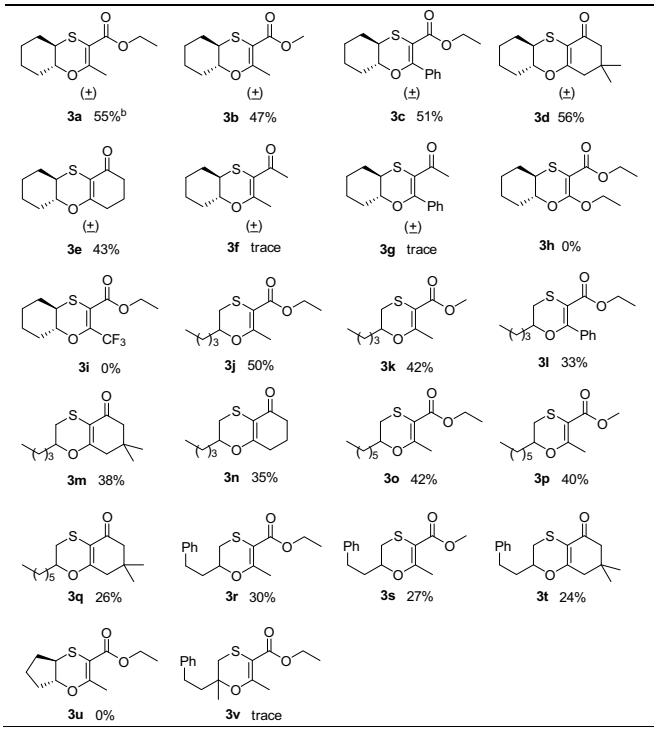
[a] All reactions were conducted on 0.3 mmol scale of **1a** or **2a** in 1 mL of solvent in a 10 mL microwave tube and was stirred under microwave irradiation in a sealed vessel.
[b] Yield of isolated product.
[c] Yield determined by ^1H NMR analysis using 1-iodo-4-nitrobenzene as an internal standard.
[d] Detected by GC-MS.

amount of the catalyst resulted in the decrease of the yield and the yield decreased sharply when the amount of the catalyst was decreased to 0.5 equiv. It was suggested that the equivalent amount of the catalyst was necessary in the reaction system due to the strong coordination ability of the sulfur atom in thiiranes. The sulfur atom may consume an equivalent amount of the catalyst (Table 1, entries 12–14). Solvents were screened because different solvents have different absorption of microwave energy, and finally 1,2-dichloroethane (DCE) was chosen as the best solvent. We considered whether the crystallized water in the $CuSO_4{\cdot}5H_2O$ catalyst would affect the yield, anhydrous $CuSO_4$ was tried and the results showed that only a trace amount of the product was obtained (Table 1, entry 18). 10 Equiv. of water were added into the reaction system when anhydrous $CuSO_4$ was applied as the catalyst, a yield of 39% was obtained, similar to that with $CuSO_4{\cdot}5H_2O$ as the catalyst (Table 1, entry 19). Thus, we speculated that the crystallized waters as ligands of the copper ion affected the catalytic activity of the catalyst. To attempt further optimization of the reaction, ethylene glycol which is relatively similar to water was selected as a ligand under anhydrous $CuSO_4$-assisted conditions, the final yield was 22%. However, when ethylene glycol dimethyl ether without active hydrogen or ethylenediamine were tested as ligands, no product was obtained (Table 1, entries 20–22). It can be concluded that the ligand water in the copper catalyst has a crucial effect on the reaction. Unfortunately, although the amount of water was varied or an appropriate amount of water was added to the other catalyst systems, the yield was still not improved. A number of experiments have been attempted to improve the yield through addition of different metal ligands, some acids, bases, or inorganic salts in the catalytic system, but all the attempts failed. The optimum reaction conditions were finally identified as follows: **1a/2a** = 2:1 under the catalysis of 2 equiv. of $CuSO_4{\cdot}5H_2O$ as the catalyst in DCE as solvent at 100 °C for 20 min microwave irradiation (Table 1, entry 12).

With the optimized reaction conditions, the reaction scope was then evaluated (Table 2). First, different diazo compounds **2** were examined. Methyl 2-diazo-3-oxobutanoate (**2b**) gave the desired product **3b** in a moderate yield of 47%, slightly lower than the ethyl ester. Ethyl 2-diazo-3-oxo-3-phenylpropanoate (**2c**) generated the corresponding product **3c** in a similar yield. When the diazo compound was replaced by cyclic diazodiketones, 2-diazocyclohexane-1,3-diones **2d** and **2e**, 56% of product **3d** and 43% of product **3e** were obtained, respectively. However, linear diazodiketones, 3-diazo-2,4-pentanedione (**2f**) and 2-diazo-1,3-butanedione (**2g**) only generated trace amounts of products and diethyl 2-diazomalonate (**2h**) and ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate (**2i**) failed in the reaction with thiirane **1a**. We further expanded different thiiranes **1** from 1,2-disubstituted bicyclic 7-thiabicyclo[4.1.0] heptane (**1a**) to monosubstituted thiiranes, *n*-butylthiirane (**1b**), *n*-hexythiirane (**1c**), and 2-phenylethylthiirane (**1d**). *n*-Butylthiirane (**1b**) generated the corresponding products **3j-3n** in low to moderate yields when it reacted with three diazoketoesters **2a-c** and two cyclic diazodiketones **2d,e**. Both *n*-hexylthiirane (**1c**) and 2-phenylethylthiirane (**1d**) can react with representative diazoketoesters **2a,b** and cyclic diazodiketone **2d**, yielding the corresponding products **3o-3t** in low to moderate yields. The results indicate that the yields of monosubstituted thiiranes are generally lower than those of disubstituted thiiranes, and the longer the alkyl chain, the more the yield decreased. This is possibly mainly attributed to the large ring tension in thiirane **1a**, which leads to a more favorable ring-opening reaction. Furthermore, when five-membered ring analog of thiirane **1a**, 6-thiabicyclo[3.1.0]hexane (**1e**), was attempted to react with ethyl 2-diazo-3-oxobutanoate (**2a**), the corresponding product **3u** was not observed. For 1,1-disubstituted 1-methyl-1-(2-phenylethyl)thiirane (**1f**), only a trace

Table 2
The scope of substrates.[a]





[a] Reaction conditions: Diazo compounds **2** (0.3 mmol) and thiiranes **1** (0.6 mmol) were added in DCE (1.0 mL) in a 10 mL microwave tube, then $CuSO_4{\cdot}5H_2O$ (0.6 mmol) was added, and the reaction mixture was stirred at 100 °C for 20 mins under microwave irradiation in a sealed vessel. All yields are isolated yields.

amount of product **3v** was obtained possibly due to the steric hindrance of 1,1-disubstituted thiirane.

In the previous report,[13] Capozzi and coworkers synthesized *cis*-1-(3-methyl-4a,7,8,8a-tetrahydro-6*H*-pyrano[2,3-*b*][1,4] oxathiine-2-yl)ethan-1-one by the hetero-Diels-Alder reaction of 2,4-dioxopentane-3-thione and dihydropyrane and determined two hydrogen atoms at the positions 4a and 8a were in *cis*-configuration. Moreover, Lacour and his coworkers prepared bicyclic 1,4-dioxene derivatives with the two hydrogens at their positions 4a and 8a in *cis*-configuration.[14] However, after carefully analyzing the coupling constants (J_{ab} > 10 Hz) between the positions 4a and 8a of products **3a-3e**, we identified the two hydrogens at the positions 4a and 8a should be *trans*. In other words, products **3a-e** are 2-substituted *trans*-3-acyl-4a,5,6,7,8,8a-hexahydrobenzo[*b*][1,4] oxathiines. To further verify our stereochemical assignment, we cultivated single crystals of solid product **3c** and determined its single crystal X-ray diffraction analysis (Fig. 2).[17] The results are consistent with the assigned stereostructure identified by ^{1}H NMR analysis. At this point, we can be pleased to say that it is the first time that we synthesized ethyl *trans*-3-acyl-4a,5,6,7,8,8a-hexahydrobenzo[*b*][1,4]oxathiines.

After obtaining the above information, we proposed the following mechanism, the reaction of cyclic thiirane **1a** and diazo compound **2a** is selected as an example to illustrate the mechanism (Scheme 3). First, diazo compound **2a** reacts with the metallic copper catalyst to form a metal carbene intermediate **A** by loss of nitrogen. Then thiirane **1a** as a nucleophile attacks the

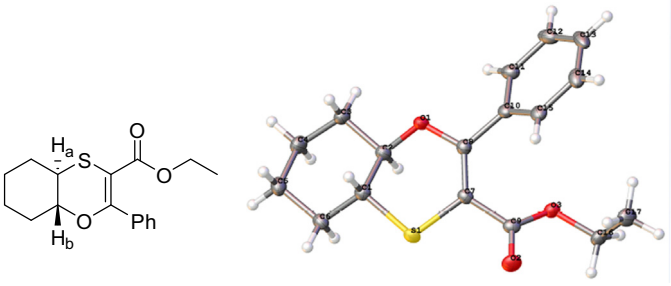
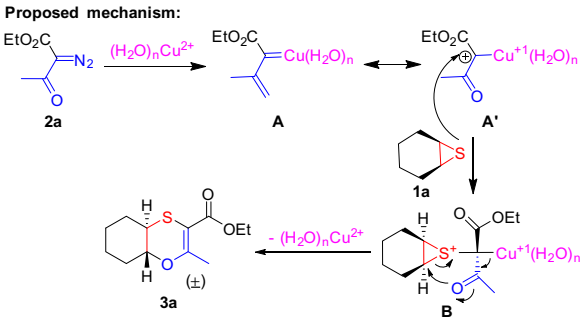


Fig. 2. Single crystal structure of ethyl *trans*-2-phenyl-4a,5,6,7,8,8a-hexahydrobenzo[*b*][1,4]oxathiine-3-carboxylate (**3c**).



Scheme 3. Mechanistic rationale.

intermediate **A** and further generates a metal sulfonium ylide intermediate **B**. Accompanied by the departure of the copper complex, the original ketonic carbonyl isomerizes into an enolate, which attacks the thiirane from the backside of the C—S bond to cause the cleavage of the C—S bond and to generate the ring expansion product **3a**. During the ring-opening reaction, the configuration of the attacked carbon is inverted as the enolate anion attacks from the back of the three-membered ring, and finally the *trans*-configuration of product **3a** is obtained. For monosubstituted thiiranes, since the thiirane ring in the intermediates **B** is partially positively charged, the enolate anion is more nucleophilic to attack the carbon atom with more substituents,[15,16] and 6-substituted products **3j-3t** are generated.

Conclusions

In summary, we developed a direct and simple strategy for the preparation of 3-acyl-5,6-dihydro-1,4-oxathiines. The method mainly utilized the reaction of α-diazo-β-1,3-dicarbonyl compounds and thiiranes under microwave and copper sulfate assistance, affording 3-acyl-5,6-dihydro-1,4-oxathiines and *trans*-3-acyl-5,6-dihydro-1,4-oxathiines from *cis*-1,2-disubstituted thiiranes. An intramolecular S_N2 mechanism was proposed for the ring expansion of thiiranes. The method also had the advantages of cheap catalyst, easy access to raw materials, short reaction times, simple operation.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.03.039. These data include MOL files and InChiKeys of the most important compounds described in this article.

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