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Synthesis of δ-thiolactams by the aza-Diels–Alder reaction of in situ generated allenyltrimethylsilylthioketenes with imines

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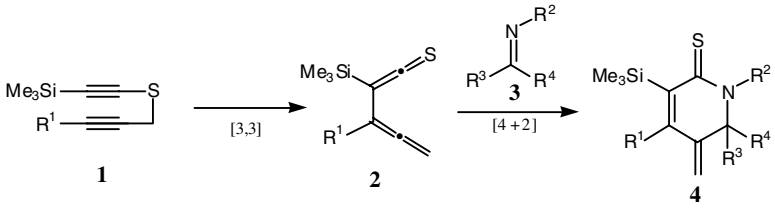
Abstract—Allenyltrimethylsilylthioketenes, generated in situ through [3,3] sigmatropic rearrangement of trimethylsilylethynyl propargyl sulfides, underwent facile [4+2] cycloaddition with imines to afford the corresponding δ-thiolactams. The resulting 2-trimethylsilyl-4-methylenetetrahydroquinolidine-2-thione, obtained by the [4+2] cycloaddition using piperideine as a dienophile, was transformed into (±)-lupinine in six steps.

The [4+2] cycloaddition of dienes and imines,[1] including catalytic asymmetric cycloaddition,[2,3] has been widely studied in the light of their synthetic utilities for the short access to indolizidines and quinolizidines of biological relevance. In many cases, Danishefsky's diene and the related dienes were employed for the required functionalities of the target products.[1,3] Recently, aza-Diels–Alder reactions of trialkylvinylketenes with *N*-trimethylsilyl imines were reported,[4] but the multi-step access to trialkylsilylketenes involving the Curtius rearrangement or the ring opening of cyclobutenone caused a limitation of the synthetic utility and versatility of the method. In our laboratory, generation of allenylchalcogenoketenes by the [3,3] sigmatropic rearrangement of alkynyl propargyl chalcogenides was established by a trapping experiment using secondary amines to provide α,β,γ,δ-unsaturated chalcogenoamides.[5] We envisaged that allenyltrimethylsilylchalcogenoketenes, composed of nucleophilic allylsilane moieties and electrophilic chalcogenoketene moieties would serve as highly-reactive dienes for polarized dienophiles, especially for an imine (Eq. 1). In this letter, we wish to describe a simple and are efficient preparation of unsaturated δ-thiolactams through [4+2] cycloaddition of allenyltrimethylsilylthioketenes **2** and imines **3**. An efficient synthesis of (±)-lupinine[6] by using the cycloaddition of **2** as the key step is also reported.



1 2 4 (1)

At the outset, we examined the [4+2] cycloaddition of allenyltrimethylsilylthioketenes **2** generated by the [3,3] sigmatropic rearrangement of trimethylsilylethynyl propargyl sulfides **1** with a variety of imines. Trimethylsilyl propargyl sulfide **1a**, which underwent [3,3] sigmatropic rearrangement even at rt, was prepared in situ by sequential treatment of trimethylsilylacetylene in THF with (1) *n*-BuLi (1.1 equiv); (2) elemental sulfur (1.1 equiv) and (3) propargyl bromide (1.1 equiv) at 0 °C. Then, an imine (0.5 equiv) was added to the reaction mixture at 0 °C, and the reaction temperature was

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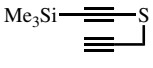
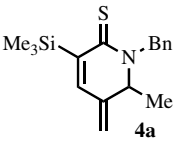
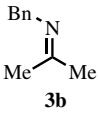
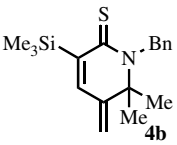
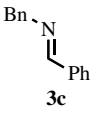
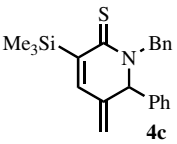
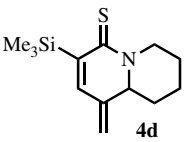
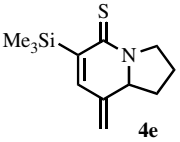
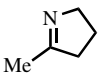
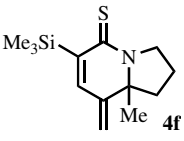
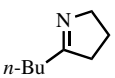
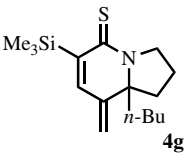
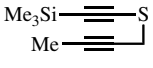
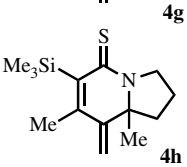
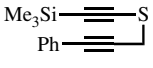
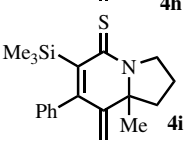
elevated to rt and the reaction mixture was stirred at rt for 12 h (Table 1, entries 1–7). Sulfides **1b** and **1c**, prepared in the analogous procedure reported for selenides,[5a,b] were heated in benzene at refluxing temperature in the presence of an imine (0.5 equiv) (Table 1, entries 8 and 9), and the crude products were purified by column chromatography on silica gel to afford cycloadducts **4** as air-stable yellow compounds. All the results are summarized in Table 1.

The structures of **4** were fully confirmed by MS, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. In the ^{1}H NMR spectra of **4a**–**g**, a set of characteristic signals assigned to a vinylic proton and two *exo* methylene protons of **4** were observed, and the ^{13}C NMR signals assigned to thiocarbonyl carbon of **4** were also observed at 187–194 ppm. The structures of δ-thiolactams **4** were finally confirmed by the X-ray crystallographic analysis of **4i**, and the ORTEP drawing of **4i** is shown in Figure 1.[7]

Table 1. Aza-Diels–Alder reaction of in situ generated allenyltrimethylsilylthioketene **2** and imine **3**

Entry	Sulfide **1**	Imine **3**[a]	Solvent	Temperature (°C)	Time (h)	Product	Yield[b] (%)
1	 **1a**[c]	 **3a**	THF	0–rt	12	 **4a**	75
2	**1a**[c]	 **3b**	THF	0–rt	12	 **4b**	35
3	**1a**[c]	 **3c**	THF	0–rt	12	 **4c**	3
4	**1a**[c]	 **3d**[d]	THF–Et_2O	0–rt	12	 **4d**	78
5	**1a**[c]	 **3e**[d]	THF–Et_2O	0–rt	12	 **4e**	66
6	**1a**[c]	 **3f**	THF	0–rt	12	 **4f**	77
7	**1a**[c]	 **3g**	THF	0–rt	12	 **4g**	56
8	 **1b**	**3f**	Benzene	Reflux	14	 **4h**	74
9	 **1c**	**3f**	Benzene	Reflux	14	 **4i**	82

[a] 0.5 M amount to **1**.

[b] Isolated yield based on the imine used.

[c] Prepared in situ by the sequential treatment of trimethylsilylacetylene with *n*-BuLi (1.1 equiv), elemental sulfur (1.0 equiv) and propargyl bromide (1.1 equiv) at 0 °C in THF.

[d] Prepared according to the reported procedure[9] and the etherial solution of the crude imines **3d** and **e** were used without concentration and purification.

It is worth noting that **2** underwent facile cycloaddition with a highly regioselective mode without the formation of β-thiolactams[8] in all cases.[4a] Treatment of allenylphenylthioketene, generated in an analogous procedure using phenylacetylene in place of trimethylsilylacetylene, with 2-methylpyrroline **3f** afforded neither [4+2] cycloadduct **4** nor [2+2] cycloadduct, as expected. This result indicates the essential role of trimethylsilyl group in the present [4+2] cycloaddition. Advantageously, piperideine **3d** and pyrroline **3e**[9] could be employed to this reaction as dienophiles under the mild reaction conditions without trimerization (Table 1, entries 4 and 5). The cycloadducts derived from these cyclic imines would serve as precursors for a variety of indolizidine or quinolizidine alkaloids. In contrast with the cases of trialkylsilylvinylketenes,[4a] the cycloadditions of allenyltrimethylsilylthioketenes **2** underwent facile cycloaddition with *N*-alkyl imines **3** having protons α to the imino group. However, the use of aryl aldimine **3c** for the dienophile gave a poor result (Table 1, entry 3), and neither *N*-Ts nor *N*-PMP derivatives of these imines **3b** and **3c** was effective for cycloaddition with **2**.

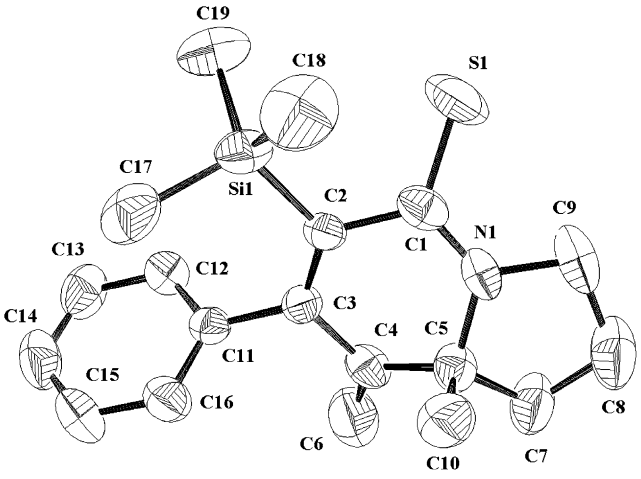
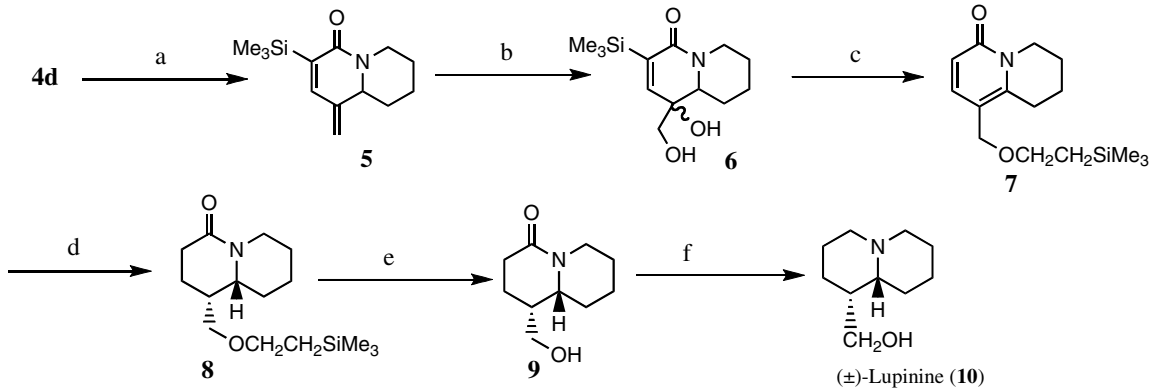


Figure 1. ORTEP drawing of thiolactam **4i**.

To demonstrate the synthetic utility of the aza-Diels–Alder reaction, we attempted the transformation of thiolactam **4d** into (±)-lupinine as shown in Scheme 1. To the best of our knowledge, the synthesis of lupinine using the aza-Diels–Alder reaction as the key step was not reported. Thus, **4d** was treated with *m*CPBA (2.0 equiv) in $CHCl_3$ at 0 °C–rt for 30 min to afford corresponding lactam **5** in 72% yield.[10] The regioselective olefin oxidation of **5** by using NMO in the presence of OsO_4 catalyst (2 mol %) furnished diol **6** in 75% yield as a single diastereomer. The subsequent treatment of **6** with TsOH (2.0 equiv) in the presence of 2-trimethylsilylethanol (2.5 equiv) afforded tetrahydroquinolidin-1-one **7** in 76% yield through desilylation, dehydration and protection in a one-pot procedure. However, a similar reaction using BnOH (2.5 equiv), in place of 2-trimethylsilylethanol, afforded the corresponding benzyl ether in 22% yield, and an analogous reaction without the use of alcohol only gave 3-hydroxymethyltetrahydroquinolidin-1-one in a much very low yield. Protected tetrahydroquinolidin-1-one **7** underwent hydrogenation in the presence of a catalytic amount of PtO_2 leading to **8** quantitatively,[11] and the subsequent deprotection of **8** by the treatment of BF_3OEt_2 afforded **9** in 64% yield as a single isomer.[12] The relative stereochemistry between the bridgehead methine protons and the oxymethylene groups in **8** and **9** were determined to be *anti* by NOE experiments. Finally, reduction of **9** by $LiAlH_4$ gave (±)-lupinine **10** in 92% yield, and the spectral data of synthetic **10** were identical with those reported.[6c]

In conclusion, we developed a novel aza-Diels–Alder reaction of allenyltrimethylsilylthioketenes **2** and imines **3** to provide unsaturated δ-thiolactams **4**. Especially, thiolactam **4d**, derived from piperideine **3d**, was converted into (±)-lupinine **10** in six steps, and the synthetic potentiality of the [4+2] cycloaddition protocol using **2** as convenient access to the precursors for variety of naturally-occuring alkaloids is just demonstrated. Further application of this methodology for the synthesis of various polycyclic alkaloids is now in progress in our laboratory.



Scheme 1. Reagents and conditions: (a) *m*CPBA (2.0 equiv), $CHCl_3$, 0 °C–rt, 30 min, 72%; (b) NMO (2.2 equiv), OsO_4 (2.0 mol %), dioxane–H_2O (v:v = 1:1), rt, 12 h, 75%; (c) $Me_3SiCH_2CH_2OH$ (2.0 equiv), TsOH (2.5 equiv), reflux, 5 h, 76%; (d) H_2 (75 psi), PtO_2 (5 mol %), MeOH, rt, 14 h, quant.; (e) $BF_3 \cdot OEt_2$ (1.2 equiv), CH_2Cl_2, 0 °C–rt, 1 h, 64% and (f) $LiAlH_4$ (1.0 equiv), Et_2O, reflux, 1 h, 92%.

References and notes

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7. Crystal data for **4i**: $C_{19}H_{25}NSSi$, $M_w = 327.56$, yellow prism, monoclinic, $P2_1/n$ (#14), $a = 10.94(3)$, $b = 10.40(4)$, $c = 17.05(6)$ Å, $\beta = 104.296(6)°$, $V = 1879(10)$ Å^3, $Z = 4$, $D_{calcd} = 1.16$ g/cm^3, $\mu(\text{MoK}\alpha) = 2.33$ cm^{-1}, $R = 0.078$, $R_w = 0.090$. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC612745.
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