

α,β -Unsaturated thioacylsilanes as efficient dienes in hetero Diels–Alder reactions

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Abstract

Reaction of several α,β -unsaturated thioacylsilanes with in situ generated thioaldehydes and thioacylsilanes affords under mild conditions a clean and regioselective access to 2-substituted 4-silyl-1,3-dithiacyclohex-4-ene derivatives, arising from an hetero-Diels–Alder reaction between two different thiocarbonyl compounds.

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The Diels–Alder reaction represents one of the most powerful and versatile methods for the construction of cyclic systems [1]. Although the majority of the reported reactions deals with cycloadditions of 1,3-dienes with ethylenic and acetylenic dienophiles to obtain carbocyclic systems, the replacement of carbon atoms in the diene or in the dienophile with heteroatoms has more recently attracted much attention, and affords a very useful method for the synthesis of six-membered heterocycles, through an hetero-Diels–Alder (HDA) reaction [2].

In this context, several heterodienes and heterodienophiles containing heteroatoms such as phosphorus, silicon, oxygen, sulfur and selenium have been investigated [2], and among them, those bearing a C=S double bond have been largely employed as the 2π group in the dienophile, due to their high reactivity towards cycloaddition processes [3].

Some of the six-membered heterocycles obtained thereby are known as useful intermediates for the synthesis of different molecules, including carbocycles [3e,4] and thia-analogues of natural products [5].

On the other hand, α,β -unsaturated thiones can also participate as 4π -heterodiene partners in inter- and intramolecular hetero-Diels–Alder reactions with activated dienophiles [6], but in all the reported examples β -substituted α,β -unsaturated thiocarbonyls have been employed, due to the difficulties in synthesizing the unsubstituted ones [7].

To the best of our knowledge only the cycloaddition of a simple α,β -unsaturated thiocarbonyl compound has been reported by several authors, namely the self-dimerization reaction of thioacrolein, that leads to isolation of regioisomeric dithiin systems [6c,8].

Our long-dated interest in the synthesis and reactivity of acylsilanes [9a,9b], and, more recently of unsaturated acylsilanes [9b,9c] prompted us to point our attention on the synthesis and the chemical behaviour of their sulfur analogues [10], thioacylsilanes, which appeared very attracting molecules, because they couple the high reactivity of the carbon–sulfur double bond with the peculiar reactivity of organosilanes, thus enabling the synthesis of various products containing the Si–C–S unit. Moreover, thioacylsilanes can serve as synthetic equivalents of thioaldehydes through a simple protodesilylation reaction.

In this connection, we recently reported a convenient novel synthetic access to thiopropenoylsilanes, through the exposure of the parent allenes **1** to HMDST

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(hexamethyldisilathiane) and CoCl_2 [11], leading to unsubstituted thiopropenoylsilanes, synthetic equivalents of thioacrolein, which undergo in the reaction medium, a self-dimerization reaction to give 1,2-dithiins **2** (Scheme 1).

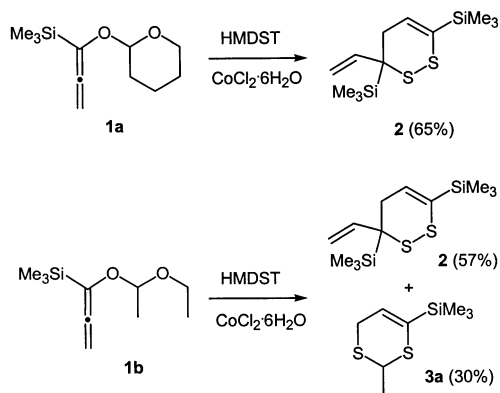
Furthermore, although thiopropenoylsilane can be considered a synthetic equivalent of thioacrolein, the regiochemical outcome of the present reaction proved to be quite different, affording as the predominant compound the head-to-head dimer instead of the 1,3-dithiin, usually obtained as the largely predominant isomer upon generation of thioacrolein, thus outlining the importance of the silyl moiety in driving the outcome of the reaction, and evidencing thioacylsilanes as a class of molecules with their own peculiar behaviour.

Interestingly, during this investigation we came across an unexpected result, in that, when reacting allene **1a**, a clean yield of the self-dimerization product **2** as the major compound was obtained, but when the open-chain protected allene **1b** was reacted, a 1:1 mixture of the expected self-dimerization product **2**, together with compound **3a** [11], was isolated (Scheme 1).

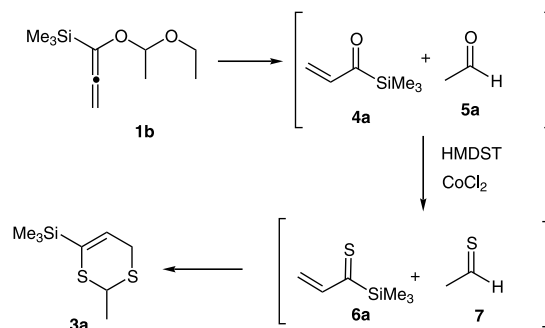
This result was quite interesting, because the only obvious explanation of the formation of **3a** seemed to be a cycloaddition reaction of the in situ generated thiopropenoylsilane **6a** with thioacetaldehyde **7**, which should arise from the acetaldehyde formed during hydrolysis of the starting allene. Tentatively, we can explain the formation of compound **3a** through the mechanism in Scheme 2.

The result of this reaction showed that thiopropenoylsilane **6a** can behave as a very efficient heterodiene [12], capable of trapping even aliphatic thioaldehydes, compounds that are known to be rather reluctant to act as heterodienophiles in the presence of acid catalysts, and to undergo preferentially oligomerization reactions [13].

It is worth noting the dramatic change in reactivity of thioacylsilanes with respect to thioacrolein, which has never been reported to participate in cycloadditions with different thiocarbonyls except self-dimerization reac-



Scheme 1.



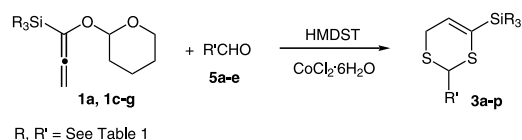
Scheme 2.

tions, and this outlines the importance of the silicon moiety in such reactional behaviour, that has also never been observed with other unsaturated thioaldehydes and thioketones. It should also be ruled out the possibility that such behaviour may be induced by the presence of CoCl_2 , this effect having never been previously observed, when generating alkanethials under the same experimental conditions [14]. Such reactions, in fact, always afforded poor yields of cycloaddition products even in the presence of different dienes.

Then, as far as the hetero-Diels–Alder reaction is a very convenient method for the preparation of six-membered heterocyclic compounds and has been widely applied to natural product synthesis, we wondered whether, under appropriate conditions, thiopropenoylsilane could behave as a thiabutadiene, capable of reacting with different transient thiocarbonyl species such as thioaldehydes and thioacylsilanes. To the best of our knowledge, no such behaviour concerning the cycloaddition of two different thiooxo compounds has ever been reported in the literature.

Thus reaction of allene **1a** with HMDST and different aldehydes, such as benzaldehyde and butyraldehyde, in a stoichiometric ratio afforded mixtures of the wanted compounds **3**, together with consistent amounts of the self-dimerization product **2** (Scheme 3).

Anyway, when reacting allene **1a** with HMDST in the presence of fivefold excess of the “external” added aldehyde, such as benzaldehyde, we were able to isolate from the reaction mixture a good yield of the corresponding cycloadduct **3b**, arising from the in situ trapping of thiobenzaldehyde by thiopropenoylsilane **6a**, together with trimers of the thioaldehyde (Scheme 3) [15]. This reaction then definitively shows that such cycloaddition between two different thiooxoderivatives can be efficiently performed.



R, R' = See Table 1

Scheme 3.

The large excess of starting aldehyde is then needed to obtain selectively the adduct **3b**, avoiding the formation of the self-dimerization product **2**.

Furthermore, with the aim to ascertain whether such behaviour could configure as a general one, we checked

such reactivity of various silylated allenes with aldehydes of different nature, both aromatic, heteroaromatic and above all aliphatic.

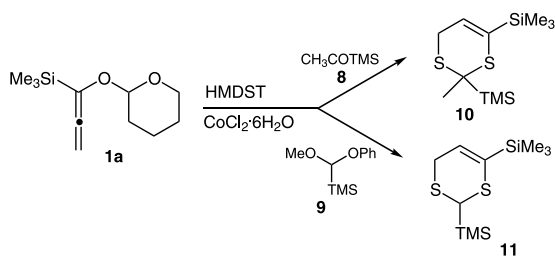
The results are summarized in Table 1.

The reaction seems quite general, and can be easily

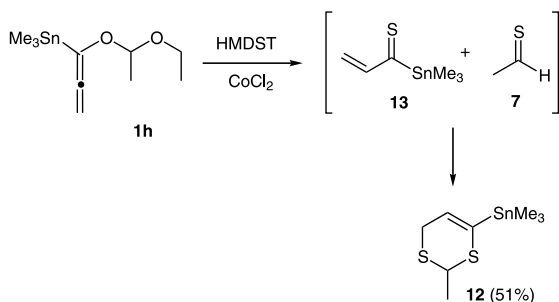
Table 1
Reactivity of silyl allenes with HMDST and thioaldehydes

Entry	SiR ₃	Reactant	Product	Yield (%) ^a
1	SiMe ₃ 1a	5a	3a	56 ^b
2	1a	5b	3b	41 ^c
3	1a	5c	3c	53
4	1a	5d	3d	48
5	1a	5e	3e	32 ^d
6	1a	8	10	36
7	1a	9	11	25
8	SiMe ₂ Ph 1c	5c	3f	32
9	SiMePh ₂ 1d	5c	3g	36
10	1d	5b	3h	26 ^e
11	SiPh ₃ 1e	5c	3i	23
12	1e	5b	3l	13
13	SiMe ₂ All 1f	5c	3m	38
14	1f	5b	3n	26 ^e
15	SiMe ₂ Cy 1g	5c	3o	35
16	1g	5b	3p	40 ^e

^a Refers to chromatographically pure material, whose spectroscopic and analytical data are consistent with the assigned structure. ^b See ref. 11. ^c 30% of 6-Phenyl-3-silyl-1,2-dithiin isomer was isolated. ^d 20% of 1,2-dithiin **2** was recovered. ^e 10–15% of 6-Phenyl-3-silyl-1,2-dithiin isomer was isolated.



Scheme 4.



Scheme 5.

performed with various in situ generated thioaldehydes, to give functionalized 4-silyl-1,3-dithiacyclohex-4-ene derivatives **3**. Furthermore, when using several silylated allenes (**1c–1g**), we found that the reactions are independent from the silyl moiety present on the starting allene (Scheme 3) (Table 1, entries 8–16), always affording the expected cycloadducts.

Thiopropenoysilanes evidence a very good reactivity also toward aliphatic thioaldehydes (entries 3, 4, 8, 9, 11, 13 and 15 in Table 1), compounds that, as previously outlined, are known to be rather inert in Diels–Alder cycloadditions [13].

It is interesting to note that in all these reactions, the regioisomer obtained has been invariably the 1,3-adduct, no trace of 1,2-isomer being ever evidenced in the crude reaction mixtures. An exception is the reaction of thiobenzaldehyde (entries 2, 10, 14, 16), in which variable amounts of 6-phenyl-3-silyl-1,2-dithiin isomer has been recovered from the reaction mixtures.

With more sterically demanding silyl moieties, such as (diphenyl)methyl- (**1d**) and triphenylsilyl (**1e**) derivatives, yields tend to decrease, although it must be remembered that these reactions are the result of three different consecutive transformations. It is nevertheless worth noting that in the present conditions, the triphenylsilyl-substituted allene **1e** proved efficient in generating the corresponding thiopropenoysilane, and in reacting with thioaldehydes (entries 11 and 12), differently from what previously observed in the generation of thiopropenoyltriphenylsilane, which did not allow the isolation of the 1,2-dithiin arising from self-dimerization, but only of polymeric material [11].

Thioacylsilanes themselves can also participate in the cycloaddition reaction (Scheme 4 and entry 6) and it is worth mentioning the other example of reactivity of acetal **9**, a synthetic equivalent of thioformylsilane [16] (Scheme 4 and entry 7).

We also tried the reaction on the stannylated allene **1h**, and to our surprise we were able to isolate the corresponding cycloadduct **12** with the in situ formed thioacetaldehyde **7** (Scheme 5) [17]. This result, besides giving further versatility to this methodology, discloses the first example of the synthesis of an α,β -unsaturated thioacetylstannane, and such compound seems also able to act as a good diene in hetero-Diels–Alder reactions.

On the other hand, different from the result obtained in the silylated series (Scheme 1) [11], in this case no traces of the self-dimerization product of thiopropenoystannane **13** were evidenced in the crude, thus showing a higher tendency of this α,β -ethylenic thioacetylstannane to react with thioacetaldehyde instead of undergoing a self-dimerization reaction.

In conclusion, we may state that thiopropenoysilanes, a novel class of organometallic derivatives, are efficient heterodienes, capable to participate in Diels–Alder cycloadditions with thioaldehydes, thus affording a novel regioselective entry to polyfunctionalized 1,3-dithiin systems.

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- [15] General procedure: To a solution of 50 mg (0.24 mmol) of allene **1a** in 1 ml of CH₃CN were added, under inert atmosphere, 107 μ l (1.2 mmol, 86 mg) of butyraldehyde, 602 μ l (2.88 mmol, 513 mg) of HMDST and 343 mg (1.44 mmol) of CoCl₂·6H₂O dissolved in 4 ml of CH₃CN. The mixture was stirred at r.t. overnight, then diluted with diethyl ether, and the organic phase was washed with water (3 \times 2 ml) and brine and dried over Na₂SO₄. Evaporation of the solvent afforded the crude product, which after purification on TLC (hexanes/diethyl ether, 40: 1) gave 30 mg of **3c** (53%). ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 0.15 (9H, s), 0.95 (3H, t, *J* = 7.4 Hz), 1.50–1.65 (2H, m), 1.80–1.91 (2H, m), 3.27 (1H, dd, *J* = 5.8, 17.6 Hz), 3.51 (1H, dd, *J* = 3.2, 17.6 Hz), 4.15 (1H, t, *J* = 7.0 Hz), 6.12 (1H, dd, *J* = 3.6, 5.9 Hz) ppm. ¹³C-NMR (50 MHz, CDCl₃) δ (ppm): –1.8, 13.7, 20.0, 28.1, 37.5, 44.8, 122.6, 135.8 ppm. MS *m/z* (%): 232 [M⁺, 15], 189 [10], 144 [15], 129 [18], 73 [100], 57 [8].
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- [17] Typical procedure: A solution of 60 mg (0.21 mmol) of allene **1h** in 1 ml of THF was added at –78 °C under N₂ atmosphere with 88 μ l (0.42 mmol, 75 mg) of HMDST and a solution of CoCl₂·6H₂O (49 mg, 0.21 mmol) in 2 ml of THF. The mixture was stirred at r.t. overnight, then diluted with diethyl ether, washed with water and dried over Na₂SO₄. Evaporation of the solvent afforded the crude product, which after purification on TLC (hexanes:diethyl ether, 40:1) gave 32 mg of **12** (51%). ¹H-NMR (200 MHz, CDCl₃) δ (ppm): 0.23 (9H, s), 1.59 (3H, d, *J* = 7.0 Hz), 3.24 (1H, dd, *J* = 6.2, 17.4 Hz), 3.58 (1H, bdd, *J* = 3.1, 17.4 Hz), 4.25 (1H, q, *J* = 7.0 Hz), 5.95 (1H, dd, *J* = 3.1, 6.2 Hz) ppm. ¹³C-NMR (50 MHz, CDCl₃) δ (ppm): –2.3, 20.9, 29.7, 30.3, 122.2, 125.5 ppm. MS *m/z* (%): 296 [8, M⁺], 281 [4], 221 [19], 165 [79], 135 [22], 71 [100].