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Improved Method for the Synthesis of β -Carbonyl Silyl-1,3-Dithianes by the Double Conjugate Addition of 1,3-Dithiol to Propargylic Carbonyl Compounds

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Abstract

$R_3\text{Si} = \text{Me}_3\text{Si}, \text{Et}_3\text{Si}, (\text{tBu})\text{Me}_2\text{Si}, (\text{Allyl})\text{Me}_2\text{Si}, (\text{Vinyl})\text{Ph}_2\text{Si},$
 $(\text{Vinyl})\text{Me}_2\text{Si}, (\text{Benzyl})\text{Me}_2\text{Si}, \text{MePh}_2\text{Si}$

Base-mediated double conjugate addition of 1,3-propane dithiol to various silylated propargylic aldehydes and ketones allows for an efficient and scalable synthesis of β -carbonyl silyl-1,3-dithianes.

Polyketide-based natural products show a tremendous variety of biological activity and structural diversity, and thus the development of new synthetic methods for their efficient syntheses has been a highly pursued goal in organic chemistry.¹ Most general and effective methods for the construction of typical polyketide motifs include an aldol reaction between enolates and aldehydes,² asymmetric allylation and crotylation of aldehydes,³ and opening of epoxides with 2-lithiodithianes.⁴ In our plan to develop a modular approach for the construction of polyketides, we

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(1)

(2)

desired to take advantage of the capacity of olefin metathesis.⁵ Thus, allylation or a crotylation product derived from bifunctional aldehyde **1** can be directly joined with another polyketide motif without any functional group manipulation. Also, it was envisioned that these processes could be further streamlined by a tandem allylation (crotylation)-epoxide opening via 1,4-Brook rearrangement, further improving the economy of polyketide synthesis (Eq 1). Such a streamlined synthesis can also be envisaged for the corresponding ketones **2** via an asymmetric aldol,⁶ Evans-Tishchenko reduction⁷ and anion relay chemistry (ARC)⁴ sequence (Eq 2). The effectiveness of this concept was amply demonstrated in our recent formal synthesis of cochleamycin A (Scheme 1),⁸ where, triethylsilyldithiane aldehyde **1** was converted to the β -

hydroxy dithiane by Leighton's asymmetric allylation.⁹ A subsequent alkylation with bromoacetaldehyde dimethylacetal under basic conditions in the presence of HMPA afforded a product, which later takes part in a tandem enyne RCM to afford an advanced intermediate in the formal synthesis of cochleamycin A.

Through this streamlined sequence, various polyketide motifs are expected to be synthesized in an unusually effective manner, which, however, is contingent upon a secure supply of carbonyl compounds **1** and **2** (Scheme 2) containing γ,δ -dithiane and trialkylsilyl moieties.

Conceptually, two general approaches (Path A and B) to these compounds are envisioned, and along these lines, several procedures^{10,11,12,13} were already reported in the literature. From the standpoint of substrate scope and functional group tolerance,^{11,12} the latter involving a double Michael addition of 1,3-propanedithiol to α,β -acetylenic aldehydes and ketones seems to be most attractive. However, the isolation of a silylated hemiacetal by Ley and coworkers under their base-mediated conjugate addition to silyl-substituted propargylic aldehydes (Eq 3) calls for an alternative procedure for silyl-substituted acetylenic aldehydes. Herein, we report on the development of a general, efficient and scalable method for the synthesis of β -carbonyl silyl-1,3-dithianes (**1** and **2**) carrying various silyl groups.

It was expected that the aldehyde **4** and ketone **6** could be garnered via formylation¹⁴ or acylation¹⁵ of the corresponding silyl acetylides. However, this route gave poor yields when lithium acetylide and silyl chlorides were employed.¹⁶ An alternative approach involves the silylation of the lithium acetylide of the commercially available THP protected propargyl alcohol, deprotection of the THP group generating alcohols **3a–k** with PPTS, and their oxidation with IBX. This three step sequence afforded aldehydes **4a–k** in good to excellent overall yields (Table 1).¹⁷ Other oxidation protocols such as Swern,¹⁸ Parikh-Doering¹⁹ or PCC oxidation led to much lower yields. Since triethylsilylacetylene is readily available at low price, the corresponding aldehyde **4b** (entry 2) was synthesized according to our initial plan involving formylation of the lithium acetylide.

Silyl-substituted methyl propargylic ketones **6a–j** were also obtained in good to excellent yields by the silylation of commercially available TMS protected 3-butyne-2-ol,²⁰ followed by desilylation with 1 M HCl, and MnO₂ oxidation²¹ of the precursor allylic alcohols **5a–j** (Table 2).

With these aldehydes and ketones **4** and **6** in hand, we attempted the addition of 1,3-propane dithiol using NaOMe as the base according to Ley's conditions.^{11c,12} As shown in Table 3, the desired dithiane aldehydes **1a** and **1b** with a trimethylsilyl (entry 1), and triethylsilyl group (entry 3) were obtained in 61 and 62% yields, respectively, whereas *t*-butyl dimethylsilyl-substituted aldehyde **1c** (entry 2) was generated in only moderate yield (42%). Further, this procedure is unlikely to be amenable to a large scale synthesis due to the necessity of large amounts (0.05 M) of solvents, which is necessary to prevent the undesired intermolecular processes. Hence, we investigated the heterogenous conditions employing MgO and basic Al₂O₃ as reported by Knight^{11d} and Ranu.^{1a} Reactions with MgO purchased from Aldrich were very slow even with 10 eq. at room temperature; only 40% of desired dithiane formed for the triethylsilyl aldehyde after 24 h together with unreacted starting material. On the other

hand, with 10 equivalents of basic alumina in CH_2Cl_2 , dithiane **1b** was obtained in 70% yield after 24 h (entry 7). Optimal yield was observed with 10 equivalents of basic Al_2O_3 in THF at 1 M concentration at room temperature. Under these conditions, substrate aldehydes **4b** and **4c** afforded dithianes **1b** and **1c** in 81 and 78% isolated yields, respectively (entries 9 and 10).

Next, an optimization for the formation of 1,3-dithianes via the addition of dithiol to the propargylic ketones was carried out with ketone substrates **6f** and **6g** that contain vinyl dimethylsilyl and benzyldimethylsilyl groups, respectively (Table 4). As expected, the propargylic ketones were much less reactive towards conjugate addition: even the reaction with 30 equivalents of Al_2O_3 gave a 1:1 mixture of double and mono conjugate addition product for the benzyldimethylsilyl ketone **6g** after 24 h at room temperature (entry 3). It was found that for these ketones, homogenous bases such as NaOMe, NaOEt and KO^tBu were more efficient (entries 5–9); addition of 0.5 equivalents of KO^tBu in $^t\text{BuOH}$ at 0 °C, followed by warming to room temperature over 3 h provided the best ratio of **6:2:7**.

After establishing these optimized reaction conditions, a range of aldehyde and ketone substrates was further examined (Table 5). Substrate aldehydes **4a–h** provided excellent yields of the corresponding products **1a–h** in the range of 48–93% yield (entries 1–8) under condition A (10 equiv. Al_2O_3 , THF, 1.5 M). Gratifyingly, reactions on 5–6 g scale of triethylsilyl and TBS-propargyl aldehydes (**4b** and **4c**) showed no diminution of yields, demonstrating the utility of these conditions. However, no conversions were observed even with 15 equivalents of Al_2O_3 for di-*tert*-butylsilyl (**4k**), *t*-butyl diphenylsilyl (**4i**), and triisopropyl (**4j**)-substituted aldehydes (entries 17–19).

Under condition B, ketones **6a–h** afforded the corresponding 1,3-dithiane products **2a–h** in good to excellent yields (entries 9–16), except for trimethylsilyl containing substrate **6a** (entry 9). The poor yield (35%) for **2a** is probably due to the instability of the trimethylsilyl group toward the alkoxide. Similar to the cases with the aldehydes, substrates **6i** and **6j** with sterically bulky silyl substituents showed either decomposition or no reaction (entries 20 and 21).

In conclusion, base-mediated conjugate addition of 1,3-dithiols to silyl-propargylic aldehydes and ketones allows for a versatile, efficient, and scalable approach towards the assembly of β -carbonyl silyl-1,3-dithianes.

Experimental Section

General procedure for dithiane aldehydes 1a–h

To a well-stirred solution of propargylic aldehydes (1 equiv) and 1,3-propanedithiol (1 equiv) in THF (1.5 M with respect to aldehyde) was added activated basic alumina (5–10 equiv, standard grade, ~150 mesh, 58 Å) in 10 portions, such that the temperature did not go above room temperature. After completion of the reaction (3–6 h, TLC), the reaction mixture was filtered through a short plug of Celite, followed by washing of the residue with DCM (2 × 50 mL). The filtrate and the washings were evaporated to give the crude product, which was purified by column chromatography (0–5% ethyl acetate in hexanes) to yield the aldehydes **1a–h** as a light yellow oil.

General procedure for dithiane ketones 6a–6h

To a well stirred solution of propargylic ketones (1.0 equiv) and 1,3-propanedithiol (1.0 equiv) in $^t\text{BuOH}$ (0.5 M with respect to ketone) was added KO^tBu (0.5 equiv) at 0 °C and the reaction was maintained at that temperature for 1–2 h, following which it was warmed up to room temperature and kept there until the reaction was complete (TLC). The reaction was diluted with H_2O and extracted with ether. The combined ether layers were washed with water and

brine, dried over MgSO_4 , filtered, concentrated, and subjected to column chromatography (0–5% ethyl acetate in hexanes) to obtain the ketones **6a–h**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Scheme 2.

Table 1

Synthesis of silyl substituted propargylic aldehydes^a

Entry	R ₃ Si		Yield (%) ^b	Yield (%) ^b
1	Me ₃ Si	a	100	71
2 ^c	Et ₃ Si	b	8 ^d	78
3	(^t Bu)Me ₂ Si	c	98	89
4	(Allyl)Me ₂ Si	d	94	74
5	(Vinyl)Ph ₂ Si	e	52	100
6	(Vinyl)Me ₂ Si	f	55	72
7	(Benzyl)Me ₂ Si	g	61	66
8	(Me)Ph ₂ Si	h	77	65
9	(^t Bu)Ph ₂ Si	i	72	100
10	ⁱ Pr ₃ Si	j	74	68
11	(H) ^t Bu ₂ Si	k	65	85

^a Reagents and conditions: (I) (i) *n*-BuLi, THF, −78 °C, 1h; (ii) R₃Si-Cl, −78 °C to rt; (iii) PPTS, MeOH; (II) IBX, DMSO.^b Isolated yields after column chromatography.^c Aldehyde was synthesized by formylation with DMF of the lithium acetylide generated with *n*-BuLi.^d Not applicable.

Table 2

Synthesis of silyl substituted propargylic ketones^a

Entry	R ₃ Si		Yield (%) ^b	Yield (%) ^b
1	Me ₃ Si	a	72	71
2	Et ₃ Si	b	85	78
3	(^t Bu)Me ₂ Si	c	67	92
4	(Allyl)Me ₂ Si	d	74	94
5	(Vinyl)Ph ₂ Si	e	100	95
6	(Vinyl)Me ₂ Si	f	80	65
7	(Benzyl)Me ₂ Si	g	82	86
8	(Me)Ph ₂ Si	h	75	85
9	(^t Bu)Ph ₂ Si	i	74	83
10	(H) ^t Pr ₂ Si	j	78	82

^a Reagents and conditions: (I) (i) *n*-BuLi, THF, -78 °C, 1h; (ii) R₃Si-Cl, -78 °C to rt; (iii) HCl (1 M); (II) MnO₂, CH₂Cl₂.

^b Isolated yields after column chromatography.

Table 3

Optimization of reaction conditions for the addition of dithiols to propargylic aldehydes

Entry	Base (equiv)	Solvent	Time (h)	Temp (°C)	Cone (M)	Yield ^d (%)
1	4a	NaOMe (1.5)	1	-10	0.05	61
2	4c	NaOMe (1.5)	2.5	-10	0.05	42 ^c
3	4b	NaOMe (1.5)	2	-10	0.05	62
4	4b	MgO (4)	10	rt	0.5	20 ^c
5	4b	MgO (10)	24	rt	0.5	40 ^c
6	4b	Al ₂ O ₃ (5) ^d	24	rt	0.5	50 ^c
7	4b	Al ₂ O ₃ (10)	24	rt	0.5	70 ^c
8	4b	Al ₂ O ₃ (10)	10	rt	0.5	80
9	4b	Al ₂ O ₃ (10)	3	rt	1	81
10	4c	Al ₂ O ₃ (10)	5	rt	1	78
11	4c	Al ₂ O ₃ (10)	10	rt	0.5	78

^a Isolated yields after column chromatography.

^b DCM:MeOH = 4:1

^c As determined from ¹H NMR spectroscopy of the crude. The rest of the mixture was unconverted starting material.

^d Basic alumina.

Table 4

Optimization of reaction conditions for the addition of dithiols to propargylic ketones^a

Entry	Base (equiv)	Solvent	Time (h)	Temp (°C)	6:2: ^b
1	6f	THF	24	rt	0:3:1
2	6f	THF	24	rt	0:5:1 ^c
3	6g	THF	24	rt	0:1:1
4	6g	THF	24	rt	0:1:1
5	6g	THF	3	-10 to rt	0:0:1 ^d
6	6g	THF	3	-10 to rt	4:0:1 ^d
7	6g	THF	3	-10 to rt	0:1.5:1
8	6g	^t BuOH	3	0 to rt	0:8:1
9	6f	^t BuOH	3	0 to rt	0:1:0

^a All reactions were carried out at a concentration of 0.5 M. SM indicates unreacted starting material.

^b Ratios were determined from ¹H NMR spectroscopy of the crude.

^c Obtained significant amounts of unidentified products.

^d Longer reaction times led to a complex mixture as observed on TLC.

Table 5

Entry	Substrates	R ₃ Si	R ₁	Condition ^a	Products	Yield (%) ^b
1	4a	Me ₃ Si	H	A ^c	1a	89
2	4b	Et ₃ Si	H	A	1b	81
3	4c	(^t Bu)Me ₂ Si	H	A	1c	78
4	4d	(Allyl)Me ₂ Si	H	A	1d	82
5	4e	(Vinyl)Ph ₂ Si	H	A	1e	48
6	4f	(Vinyl)Me ₂ Si	H	A	1f	80
7	4g	(Benzyl)Me ₂ Si	H	A	1g	88
8	4h	(Me)Ph ₂ Si	H	A	1h	93
9	6a	Me ₃ Si	Me	B	2a	35
10	6b	Et ₃ Si	Me	B	2b	64
11	6c	(^t Bu)Me ₂ Si	Me	B	2c	100
12	6d	(Allyl)Me ₂ Si	Me	B	2d	100
13	6e	(Vinyl)Ph ₂ Si	Me	B	2e	100
14	6f	(Vinyl)Me ₂ Si	Me	B	2f	98
15	6g	(Benzyl)Me ₂ Si	Me	B	2g	92
16	6h	(Me)Ph ₂ Si	Me	B	2h	98
17	4i	(^t Bu)Ph ₂ Si	H	A ^f	-	NR ^e
18	4j	ⁱ Pr ₃ Si	H	A ^f	-	NR ^e
19	4k	(H) ⁱ Bu ₂ Si	H	A ^d	-	NR ^e
20	6i	(^t Bu)Ph ₂ Si	Me	B ^h	-	trace
21	6j	(H) ⁱ Pr ₂ Si	Me	B	-	decomp ^g

^aCondition: (A) 10 eq. Al₂O₃, THF (1.5 M); (B) 0.5 eq. KO^tBu, ⁱBuOH (0.5 M).

^bIsolated yields after column chromatography.

^c5 eq. of Al₂O₃ was optimum.

^dReaction was forced with 15 eq. of Al₂O₃.

^eNo reaction.

^f Reaction was forced with 30 eq. of Al₂O₃.

^g Decomposed.

^h Reaction was forced with 1.5 eq. of KO^tBu.