

Trimethylsilyloxide-Catalysed Peterson Olefinations with 2,2-Bis(trimethylsilyl)-1,3-dithiane

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The synthesis of the reagent 2,2-bis(trimethylsilyl)-1,3-dithiane was directly achieved in an excellent yield from 1,3-dithiane in one step. The bench-stable reagent can be utilized for Peterson olefinations using either TMSOK/Bu₄NCl or fluoride ion as promoter of α -silyl carbanion formation,

Introduction

Since the seminal reports by Corey and Seebach on temporary reversal of polarity of carbonyl groups (umpolung), 2-lithio-1,3-dithiane derivatives have been widely exploited as sulfur-stabilized acyl anion equivalents.^[1] 1,3-Dithianederived compounds have had substantial impact on natural product synthesis and in the construction of myriads of heterocycles.^[2] The synthetic potential of ketene dithioacetals 1 is also broad, because the double bond is susceptible to both electrophilic and nucleophilic transformations due to the stabilizing effect of the adjacent sulfur atoms.^[3-5] Polyfunctionalised ketene dithioacetals were first prepared from carbon disulfide and substrates bearing active methylene groups followed by alkylation of the sulfur atoms.^[6] Subsequent approaches developed for the synthesis of cyclic ketene dithioacetals 1 use various classical olefination reactions to form the C-C double bond from carbonyl groups and suitably substituted 1,3-dithiane or 1,3-dithiolane carbanions (Scheme 1). For example, Wittig or Horner-Emmons olefinations utilising the ylides 2 or 3 have been reported, though the synthesis of these ylides requires numerous synthetic operations and produce high-molecularweight by-products (Route A).^[7] Similar issues occur with the use of (2-diphenylphosphinoyl)- or (2-diphenylthiophosphinoyl)dithianes 4 (analogous to Horner-Wittig vlides), and their use is rare (Route B).^[8] Peterson olefinations have proved successful with α -silyl carbanion 5 being generated by deprotonation using strong base (e.g. BuLi) at low temperature, followed by treatment with a carbonyl compound to yield 1 (Route C).^[9] The utility of thereby generating ketene dithioacetals, which are versatile intermediates in organic synthesis. Olefination reactions were successfully achieved with aromatic, heteroaromatic, aliphatic aldehydes and ketones.

[bis(phenylthio)methyl]boronic ester 6 (Route D) is a less preferable choice owing to the laborious synthetic operation and limitation of bench stability^[10] The use of the Takai alkenation employing 1,3-dithian-2-one 7 in the presence of dibromoalkane 8, zinc and TiCl₄ are scarce (Route E).^[11]



Scheme 1. Routes for the synthesis of ketene dithioacetals 1.

Of this collection of olefination approaches, the Peterson olefination provides superior atom economy over the phosphorus reagents as it produces low-molecular-weight volatile by-products.^[12] Despite these significant merits, the Peterson olefination remains under-utilized presumably due to the additional synthetic efforts required for its use. For example, in the literature, the α -silyl carbanion 10 is typically generated by the deprotonation of 9 using strong base, e.g. BuLi (-25 °C to -78 °C), in THF, which subsequently is treated with carbonyl compound 12 to produce 1

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(Scheme 2).^[9] It has been previously reported that bis(trimethylsilane) reagents can readily participate in olefination reactions with suitable Lewis base activation; though this approach has not been adopted for ketene dithioacetal synthesis.^[13] The use of bis(trimethylsilane) compounds as Peterson olefination reagents offers an advantage in that it removes the need to pre-form the carbanion species as its equivalent is generated in situ in the presence of the aldehyde (Scheme 2). As such, the merit of using reagent **11** in olefination reactions was investigated.

Previous reports



Scheme 2. Ketene dithioacetals by Peterson olefination.

In the current paper we report on an efficient route for the synthesis of reagent **11**, its optimal C–Si bond activation with trimethylsilyloxide or fluoride for the olefination of carbonyl compounds.

Results and Discussion

At the outset of this work, the synthesis of reagent 2,2bis(trimethylsilyl)-1,3-dithiane (11) was accomplished by two related approaches. Deprotonation of 1,3-dithiane (13) with BuLi (1.2 equiv.) in THF at 0 °C and treatment with TMSCl gave 2-(trimethylsilyl)-1,3-dithiane (9) in 89% isolated yields. Repeating this reaction sequence with 9 afforded 11 in 87% yield. Remarkably, this synthesis could be streamlined into a one-pot strategy from dithiane 13 using 2.2 equiv. of BuLi in THF at 0 °C (15 min), with subsequent chlorotrimethylsilane quench giving an excellent 90% yield of product 11 (Scheme 3).^[14] Presumably, this works by first formation of 9 with rapid in situ deprotonation and conversion into 11. Compound 11 can be considered a benchstable surrogate of 10 requiring a Lewis base promoter to generate its α -silyl carbanion equivalent.



Scheme 3. Synthesis of 2,2-bis(trimethylsilyl)-1,3-dithiane (11).

With an efficient route to 11 in hand, optimization of the olefination conditions was conducted using benzaldehyde as model electrophile. Encouragingly, using 1 equiv. of CsF in DMF at room temperature for 15 h gave ketene dithioacetal 1a in a 73% yield (Table 1, Entry 1). Examination of 20 mol-% tetrabulylammonium fluoride (TBAF) and tetrabutylammonium triphenyldifluorosilicate (TBAT) as alternative fluoride activators in THF at room temperature gave lower but satisfactory yields of 1a (Table 1, Entries 2, 3). A solvent-effect study was carried out using 20 mol-% TBAT as activator in toluene, DCM and acetonitrile at room temperature; however, each gave a poorer yield than THF (Entries 4-6). Increasing the reaction temperature (10 mol-% TBAT) in either THF or toluene gave improved yields when compared to room temperature, and 1a was obtained in 72% and 83% yields, respectively, and in a shorter reaction time of 3 h (Table 1, Entries 7, 8). The use of Me₃SiO⁻/Bu₄N⁺ as a general activation reagent of organotrimethylsilanes for addition reactions has been established, though its ability to activate geminal bis(silanes) for Peterson olefinations has not been previously reported.^[15] For comparison with fluoride, TMSOK/Bu₄NCl (10 mol-%) was used as activator in toluene at 80 °C for 3 h and found to give **1a** in a comparable 81% yield (Entry 9). Notably, under ambient conditions TMSOK/Bu₄NCl (10 mol-%) gave 79% isolated yield of the olefin 1a. Collectively, from these results TBAT and TMSOK/Bu₄NCl (10 mol-%) in toluene at 80 °C were chosen as conditions to explore the substrate scope and generality of this method.

Table 1. Reaction optimization.[a]

	Me ₃ Si SiMe ₃ S S a J 7 11	Ph H ctivator (mol-%) solvent	s ·	Ph S J 1a	
Entry	Activator (mol-%)) Solvent	Т	t	Yield
			[°C]	[h]	[%]
1	^[b] CsF	DMF	r.t.	15	73
2	TBAF (20)	THF	r.t.	15	60
3	TBAT (20)	THF	r.t.	15	63
4	TBAT (20)	MeCN	r.t.	15	51
5	TBAT (20)	DCM	r.t.	15	31
6	TBAT (20)	PhMe	r.t.	15	49
7	TBAT (10)	THF	70	3	72
8	TBAT (10)	PhMe	80	3	83
9	TMSOK/Bu ₄ NCl (1	0) PhMe	80	3	81
10	TMSOK/Bu ₄ NCl (1	0) PhMe	r.t.	3	79

[a] Conditions: 11 (1.0 equiv.), benzaldehyde (1.5 equiv.) and solvent (2 mL). [b] 1.0 equiv. of CsF and MS (4 Å) used.

The substrate scope was first evaluated with a variety of enolisable and non-enolisable aromatic and aliphatic aldehydes using fluoride as activator (Scheme 4, Conditions A); *ortho-, meta-* and *para-substituted* aldehydes worked well in the presence of TBAT activator delivering the corresponding products **1b–g** in 62–90% yields (Scheme 4, Conditions A). Pleasingly, (*E*)-cinnamaldehyde was also tolerated



to give 83% yield of the unsaturated ketene dithioacetal **1h**, and sterically hindered mesitaldehyde and 2-naphthaldehyde gave **1i** and **1j** in 76% and 85% yield, respectively. Encouraged by these results, the participation of heterocyclic aldehydes was also tested. Furfurals and *N*-Boc-substituted indolecarbaldehyde reacted successfully under the established conditions providing 62–85% yield of the products **1k–m**. A representative of the metallocene class, ferrocenecarbaldehyde also proved to be an effective substrate for olefination with 81% yield of the product **1n** obtained. Gratifyingly, an enolisable alicyclic aldehyde, cyclohexanecarbaldehyde, gave a moderate yield of olefin **1o** (45%), though acetophenone failed to give the desired product. The olefination of ketones, such as benzophenone, 4-methoxybenzophenone and 2,2,2-trifluoromethylacetophenone,



Scheme 4. Scope of aldehydes and ketones.^[a] [a] Conditions: **11** (1.0 equiv.), aldehydes or ketones (1.5 equiv.), PhMe (2.0 mL). [b] 1.0 equiv. CsF, DMF (2.0 mL) and MS (4 Å) used. [c] 30 mol-% TMSOK/Bu₄NCl used.

were unsuccessful in the presence of 10 mol-% TBAT activator. Though switching to the more forcing conditions of 1 equiv. of CsF/DMF was successful giving 63–78% yield of the corresponding ketene dithioacetals **1p–r**.

To illustrate the practicality of trimethylsilyloxide-catalysed reactions, a side-by-side comparison with fluoride activation was conducted for eight carbonyl substrates (Scheme 4, Conditions B). Aromatic p-F- and p-MeO-substituted aldehydes gave 84% and 81% yield of the corresponding products 1d, g, which was comparable to those under fluoride conditions. Similar yields for ketene dithioacetals 1h, i, j, k and n were obtained from cinnamaldehyde, mesitaldehyde, 2-naphthyl-, furyl- and ferrocenesubstituted aldehydes (Scheme 4, Conditions B). A representative ketone, benzophenone, could also be induced to react with TMSOK/Bu₄NCl, though in a 42% yield - somewhat lower than under CsF/DMF conditions. Taken together, these results prove that reagent 11 is suitable for Peterson olefination with either trimethylsilyloxide or fluoride as silicon activator for the conversion of a wide set of carbonyl substrates into their corresponding ketene dithioacetals

To further asses TBAT and TMSOK/Bu₄NCl as silicon activators, a comparison of conversion over time for the reaction of **11** with benzaldehyde was carried out. Using either TBAT (10 mol-%) or TMSOK/Bu₄NCl (10 mol-%) in toluene at ambient temperature, the reaction progress was monitored for the formation of product **1a** using ¹H NMR spectroscopy. Interestingly, the reaction with Me₃SiO⁻/Bu₄N⁺ activation gave more than 90% conversion within 30 min, while TBAT reached only approximately 20% conversion within the same time (Figure 1). This result shows that Me₃SiO⁻/Bu₄N⁺ is a superior activator of **11** for the generation of its corresponding α -silyl carbanion.



Figure 1. Relative percentage formation of **1a** using TBAT (circles) or TMSOK/Bu₄NCl (triangles).

A plausible mechanistic cycle of trimethylsilyloxide-catalysed olefinations with **11** is depicted in Scheme 5. The mixing of TMSOK and Bu_4NCl results in a cation exchange producing $Me_3SiO^-Bu_4N^+$ and KCl, which has the effect of increasing the nucleophilic character of Me_3SiO^- . It could be expected that Me_3SiO^- interaction with the silicon atom

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of a TMS substituent on **11** gives rise to a hypervalent silicon species resulting in the breaking of a carbon–silicon bond with the generation of carbanion **10** and hexamethyldisiloxane (HMDS). Addition of **10** to the carbonyl compound would form alkoxide **13**, which upon elimination of Me₃SiO⁻ produces product **1** and regenerates the catalyst (Scheme 5). To confirm that the solvent HMDS (Me₃SiO-SiMe₃) with low molecular boiling point was formed as the final by-product, the reaction of **11** and benzaldehyde was conducted in [D₈]toluene with monitoring of the ¹H NMR chemical shifts between $\delta = -0.1$ and 0.4 ppm (Figure 2). It was seen that the sole TMS-containing by-product with a resonance at $\delta = 0.10$ ppm was Me₃SiOSiMe₃, which was



Scheme 5. Trimethylsilyloxide-catalysed Peterson olefination.

It was also confirmed that HMDS was the by-product when TBAT (10 mol-%) was used as the activator indicating that fluoride acted as reaction initiator with an autocatalytic cycle involving Me_3SiO^- also participating (Figure 2, Panel C).^[16]



Figure 2. ¹H NMR spectra in $[D_8]$ toluene. (A) Substrate **11** + benzaldehyde; (B) TMSOK/Bu₄NCl (10 mol-%) reaction; (C) TBAT (10 mol-%) reaction; (D) authentic sample of HMDS.

Conclusions

The one-pot synthesis of 2,2-bis(trimethylsilyl)-1,3-dithiane (11) as a bench-stable Peterson olefination reagent was achieved in excellent yield. The mild activation of 11 using either trimethylsilyloxide or fluoride induced a Peterson olefination sequence with aldehydes and ketones to deliver the corresponding ketene dithioacetals in good to excellent yields. ¹H NMR analysis indicates that trimethylsilyloxide acts as a catalyst for the reaction, and fluoride initiates the reaction with trimethylsilyloxide contributing in an autocatalysis manner. Further studies of the use of geminal bis-(trimethylsilane)s for olefination reactions is ongoing and will be reported on in due course.

Experimental Section

General Procedure for the Olefination of 2,2-Bis(trimethylsilyl)-1,3dithiane (11) with Carbonyl Compounds: A solution of 11 (0.50 mmol) and aldehydes or ketones (0.75 mmol) in toluene (2.0 mL) was treated with TMSOK and Bu_4NCl (0.05 mmol) or TBAT (0.05 mmol) under N₂, and the resulting solution was heated at 80 °C for 3 h. The reaction mixture was cooled to room temp., the solvent removed under reduced pressure, and 2 M HCl (15 mL) added. The residue was extracted with diethyl ether (15× 3 mL), the organic layers were combined, washed with brine, dried with Na₂SO₄ and concentrated to dryness. Purification by aluminum oxide chromatography eluting with cyclohexane/ethyl acetate gave the corresponding ketene dithioacetal.

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