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Letter

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Novel Route to Triethylsilyl-Substituted Cyclopropanes

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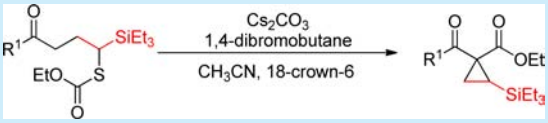
Supporting Information

ABSTRACT: Radical adducts of *S*-α-ketonyl dithiocarbonates (xanthates) to triethyl vinylsilane are converted into triethylsilyl-substituted cyclopropanes upon ozonolysis followed by exposure to 1,4-dibromobutane and Cs_2CO_3/18-crown-6 in refluxing acetonitrile. The sequence works best with phenacyl type adducts, and the use of the less bulky trimethysilyl (TMS) derivatives results in extensive desilylation.



Cyclopropanes, the smallest of the cycloalkanes, display a unique reactivity that continues to fascinate organic chemists. Many cyclopropane-containing natural products exhibit remarkable biological activity or have particularly unusual structures. The pyrethrins, for example, have acted as key lead structures for numerous synthetic insecticides built around the chrysanthemic acid motif representing a billion-dollar industry.[1a] The duocarmycins are potent DNA alkylating agents that have inspired a vast amount of work in search of clinically useful antitumor drugs.[1b−d] FR-900848 and U-106305 are two very unusual natural products isolated from a streptomyces strain and featuring four and five contiguous cyclopropane rings, respectively.[1e−h] The increasing interest in cyclopropanes has spurred the development of numerous synthetic routes to these strained structures.[2] The majority of the approaches rely on variants of the following reactions: the Simmons−Smith cyclopropanation, the transition-metal catalyzed cyclopropanations of alkenes with diazo compounds, and the Corey−Chaykovsky reaction and variants thereof. In the present letter, we describe a new convergent route to cyclopropanes with two geminal electrophilic groups that is particularly suited to the synthesis of silyl substituted derivatives, a relatively rare class of compounds the chemistry of which has hardly been explored.

In previous work, the groups of Maas and France employed (trimethylsilyl)diazomethane as the silicon source and a polymeric ruthenium(I) complex and copper(I) bisoxazoline species as the catalysts, respectively, to obtain diverse silicon-substituted cyclopropanes from the corresponding alkenes.[3] Straub and Marko, in contrast, reacted a number of diazoalkanes with various alkenylsilanes, under a low loading of $Pd(OAc)_2$, to generate a series of cyclopropylsilanes.[4] Takai's team also reported a method to prepare cyclopropylsilanes, whereby treatment of terminal alkenes with Me_3SiCHI_2 and organochromium reagents gave cyclopropylsilanes in good yield.[5] Gevorgyan and co-workers developed the first highly efficient, diastereo- and regioselective transition-metal-catalyzed addition of silanes to cyclopropenes.[6] Ito and Sawamura described a protocol for the synthesis of optically active boron−silicon bifunctional cyclopropane derivatives through enantioselective copper(I)-catalyzed reaction of allylic carbonates with a diboron derivative.[7] Recently, Charette and co-workers exposed di-*tert*-butoxy(alkenyl)silanols to 2 equiv of the preformed zinc carbenoid bis(iodomethyl)zinc $[Zn(CH_2I)_2]$ in a Simmons−Smith cyclopropanation reaction furnishing the corresponding di-*tert*-butoxy(cyclopropyl)silanols in excellent isolated yields.[8]

Over the past few years, we have disclosed unconventional approaches to a variety of highly functionalized scaffolds of potential synthetic or pharmacological interest, such as dienes,[9] pyrroles,[10] thiophenes,[11] dihydrothiazines,[12] 1,3-dithietanones,[13] ketene monothioacetals,[14] and thieno[2,3-*b*]-thiopyran-4-ones,[15] combining the radical and nonradical chemistries of xanthates. This alliance offers both flexibility and convergence and allows the introduction of tremendous diversity into the structures. We have now considered the possibility of rapidly constructing the synthetically interesting but hitherto not readily accessible cyclopropylsilylanes substituted by two different electron-withdrawing groups. Our three-step approach, outlined in Scheme 1, involves (1) intermolecular radical addition of xanthate **1** to terminal alkene **2**; (2) conversion of xanthate **3** into thiolcarbonate **4** by ozonolysis;[16] an (3) intramolecular transformation into cyclopropane **5**.

In an alkaline environment, ketone **4** is in equilibrium with its enolate **6**, and the proximity of the latter to the thiolcarbonate group should encourage a nucleophilic attack on the carbonyl group leading to intermediate **7**, which should in turn readily evolve into open form **8**. By adding 1,4-dibromobutane into the mixture, the thiolate anion should be selectively captured and converted into sulfonium intermediate **9**. In this manner, a good leaving group is created which can be substituted by the enolate in **10** to finally furnish the desired cyclopropane **5**.

To give this complex sequence the best chance of success, we decided initially to prepare a cyclopropane without the silyl group. Thus, we treated xanthate **1a** and 1-heptene **2a** with a small amount of lauroyl peroxide (DLP) in refluxing ethyl acetate and obtained the desired xanthate **3a** in 83% yield as a

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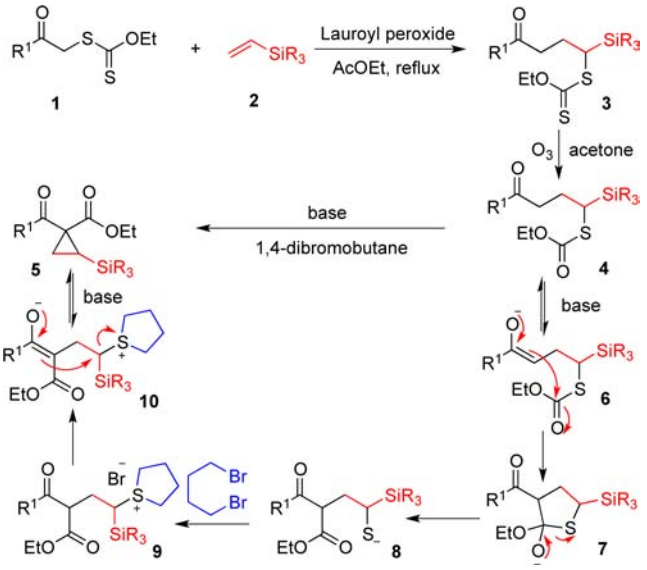
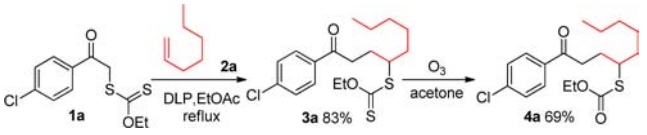
Scheme 1. General Strategy and Mechanism for Cyclopropane Formation



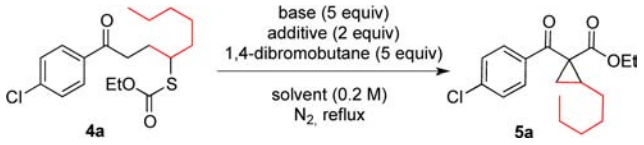
pale yellow oil. This xanthate was then converted into thiolcarbonate **4a** by ozonolysis in order to eliminate any interference by unwanted sulfur nucleophiles arising from the thiono group. This was accomplished by exposing xanthate **3a** in acetone to a stream of ozone at room temperature for a few minutes, furnishing the desired thiolcarbonate **4a** in 69% yield (Scheme 2).

Scheme 2. Synthesis of Starting Thiolcarbonate 4a



With the thiolcarbonate **4a** in hand, we were able to turn our attention to the intramolecular rearrangement−cyclopropanation process through the formation of cyclic tetrahydrothiophenonium salts as the leaving group.[17] First, we treated thiolcarbonate **4a** with 10 equiv of K_2CO_3 as the base and 5 equiv of 1,4-dibromobutane as the electrophile in CH_3CN/*t*-BuOH (9/1) under reflux in a nitrogen atmosphere for 24 h. After workup, we obtained the desired cyclopropane **5a** in only 42% yield as a mixture of two isomers (1:1, as estimated by NMR) (Table 1, entry 1). We noticed, however, that K_2CO_3 did not dissolve well in the CH_3CN/*t*-BuOH solvent combination. We therefore decided to use 2 equiv of 18-crown-6 to replace *t*-BuOH as the additive to promote the solubility of K_2CO_3 in CH_3CN. The thiolcarbonate **4a** was totally consumed after 10 h of reflux, affording a 74% isolated yield of cyclopropane **5a** (Table 1, entry 2). We nevertheless felt that the yield could still be improved, even though thiolcarbonate **4a** was totally consumed. We assumed that **4a** was indeed converted into the intermediates displayed in Scheme 1 but that the evolution into the desired cyclopropane **5a** was not complete. Unfortunately, prolonging the reaction time to 24 h furnished an even lower yield (60%) (Table 1, entry 3). We also screened LiOH and $KHCO_3$ as the bases, but after 24 and 40 h reflux respectively in CH_3CN and in the presence of 18-crown-6, both of these conditions resulted in a very poor yield (Table 1, entries 4 and 5). With the soluble organic base, DBU, in CH_3CN, the reaction did not proceed at all (Table 1, entry 6). Finally, we tested cesium carbonate, which has better solubility in acetonitrile and is a stronger base than potassium carbonate. Under the same conditions, except that 5 equiv of cesium carbonate were used in place of potassium carbonate, thiolcarbonate **4a** was smoothly transformed into the desired product **5a** in 86% yield and in the same epimeric ratio. Moreover, the reaction time was shortened to 1.5 h (Table 1, entry 7). We also attempted to run this reaction without 18-crown-6; however, the yield decreased to 80%, and the reaction time increased to 5.5 h (Table 1, entry 8). Finally, we adopted as the optimized cyclopropanation conditions 5 equiv of Cs_2CO_3 as the base, 5 equiv of 1,4-dibromobutane as the electrophile, and 2 equiv of 18-crown-6 as the phase-transfer catalyst in CH_3CN (0.2 M) under reflux in a nitrogen atmosphere.

Table 1. Optimization of the Reaction Conditions



entry	base	solvent	additive	time (h)	yield[a] (%)	dr[b]
1	K_2CO_3	*t*-BuOH/ CH_3CN		24	42	1:1
2	K_2CO_3	CH_3CN	18-crown-6	10	74	1:1
3	K_2CO_3	CH_3CN	18-crown-6	24	60	1:1
4	LiOH	CH_3CN	18-crown-6	24	trace	nd
5	$KHCO_3$	CH_3CN	18-crown-6	40	trace	nd
6	DBU	CH_3CN		24	nr	nd
7	**Cs_2CO_3**	**CH_3CN**	**18-crown-6**	**1.5**	**86**	**1:1**
8	Cs_2CO_3	CH_3CN		5.5	80	1:1

[a]Isolated yield; nr = no reaction. [b]The dr was determined by NMR; nd = not detected.

With these reaction conditions in hand, we next examined the applicability of this process to the synthesis of silyl-substituted cyclopropanes. Under the standard conditions for the radical addition of xanthates and ozonolysis into thiolcarbonates, we prepared **3b** and **4b** in 96% and 80% yield, respectively (Scheme 3). In the event, we obtained the desired trimethylsilyl (TMS) substituted cyclopropane **5b** but in only 35% isolated yield and as two epimers (dr = 5:1) although the thiolcarbonate **4b** was totally consumed after 2 h reflux. We also isolated 22% yield of a side product arising from desilylation of **5b** (H instead of TMS). As an extension of this exploration, we also prepared aliphatic substituted xanthate **3c** in 91% yield and thiolcarbonate **4c** in 78% yield. Under identical conditions for the cyclopropanation, thiolcarbonate **4c** reacted in a similar way to give cyclopropylsilane **5c**. Compared to **4b**, **4c** gave an even lower yield of the desired TMS substituted cyclopropane **5c** (yield = 18%, dr = 1.5:1) and additional side products including 16% yield of desilylated cyclopropane (**5c**, H instead of TMS) and 29% yield of the product derived from the desilylation of the starting material (**4c**, H instead of TMS).

From the preliminary results above, we realized that the TMS group was too easily lost under the alkaline conditions. To overcome this difficulty, we attempted the reaction on the corresponding triethylsilyl (TES) substituted thiolcarbonates.

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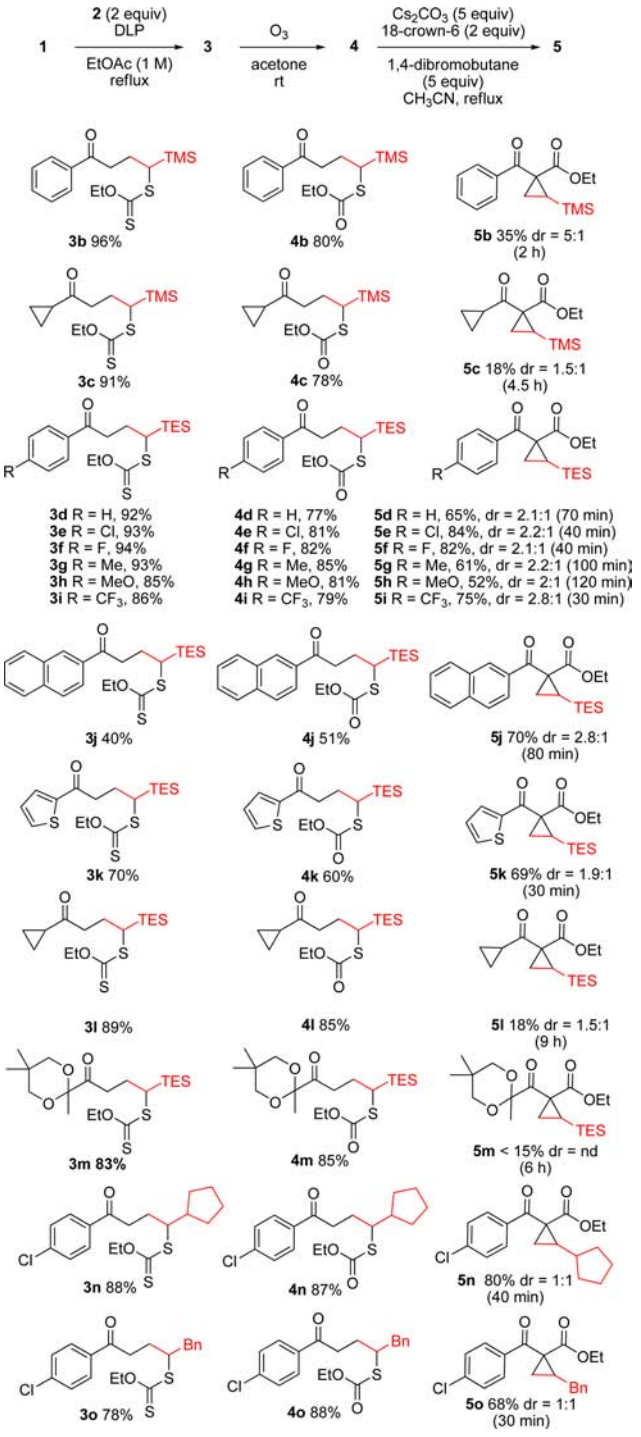
Scheme 3. Synthesis of Substituted Cyclopropanes



Larger substituents on the silicon increase resistance to protodesilylation, although the introduction of the silyl group becomes more difficult. Compared to TMS, TES is more sterically congested and resists longer against the action of cesium carbonate. Thus, following the standard xanthate addition procedure, we obtained the desired TES-substituted adduct **3d** in 92% yield, which was ozonolyzed into **4d** in good yield. We next treated the **4d** as the starting material in the cyclopropanation process. After 70 min of reflux under identical conditions, the thiolcarbonate **4d** was totally consumed, as monitored by thin-layer chromatography (TLC), and furnished the desired cyclopropylsilane product **5d** in 65% isolated yield, again as two epimers (dr = 2.1:1). This result confirmed our expectation that larger substituents on silicon would increase resistance to desilylation. We also attempted to reduce the amount of cesium carbonate to 2 equiv, but unfortunately, this decreased the yield of compound **5d** to 54% (dr = 2.4:1), and the reaction time was increased to 3 h (Scheme 3).

The radical addition step was not much affected by substitution on the aromatic ring and phenacyl xanthates with either electron-withdrawing and electron-donating groups **1** reacted efficiently with triethyl vinylsilane **2c** to give good to excellent yield of adducts (Scheme 3, **3d**−**i**). The following ozonolysis also proceeded in generally good yield (Scheme 3, **4d**−**i**). For the cyclopropanation step, we found that substrates substituted with electron-withdrawing groups, such as Cl and F, gave higher yields of products. In addition, the reaction time was reduced to 30−40 min and the ratio of the two epimers ranged from 2.1:1 to 2.8:1 (Scheme 3, **5e**, **5f**, **5i**). Substrates with electron-rich substituents provided somewhat lower yields of products and needed longer reaction times (Scheme 3, **5g**, **5h**). We encountered some difficulty with the addition of naphthyl-substituted xanthate **1h** to triethylvinylsilane in the synthesis of **3j**. We obtained the xanthate adduct in only 40% yield even when we prolonged the reaction time and added more DLP initiator. It is possible that this is due to a competing radical closure on the less aromatic naphthalene ring. The following ozonolysis step did not furnish a good yield of the thiolcarbonate either, presumably because of competing oxidation of the electron-rich aromatic ring (Scheme 3, **3j**, **4j**). However, naphthyl substituted thiolcarbonates **4j** gave 70% yield of the desired cyclopropane **5j**, again as two epimers (dr = 2.8:1) after 80 min of reaction time (Scheme 3, **5j**). The xanthate with a thiophene substituent provided a 70% yield of adduct but needed more radical initiator as well as a longer reaction time (Scheme 3, **3k**). After ozonolysis, we obtained the desired thiolcarbonate **4k** in 60% yield, which underwent cyclization under the standard conditions to furnish 69% yield of cyclopropane **5k** (dr = 1.9:1). In this case, the reaction time was shortened (30 min) as compared to **5j** (Scheme 3, **5k**).

Finally, we attempted to synthesize aliphatic cyclopropylsilanes. By analogy with the route to TMS-substituted thiolcarbonate **4c**, we prepared the TES-substituted thiolcarbonate **4l** in two steps. However, the following cyclopropanation reaction was still inefficient and sluggish, giving **5l** in only 18% yield as two epimers (dr = 1.5:1), along with 28% yield of prematurely desilylated byproduct after 9 h of reflux. We also recovered 50% of unreacted starting material **4l** (Scheme 3, **5l**). In the case of the aliphatic substrates, it appears that the slightly lower acidity and therefore slower formation of the corresponding enolates allows unwanted competing reactions to occur with a consequent decrease in yield. This was confirmed by examining thiolcarbonate **4m**, which can only enolize from the desired side, but which nevertheless also gave a low yield of cyclopropane **5m** (Scheme 3, **5m**).

While we have concentrated our efforts on the synthesis of the rare silicon-substituted cyclopropanes, this strategy is of a more general applicability. Thus, following the standard radical addition procedure, we were able to prepare **3n** and **3o** in 88% and 78% yield, respectively. Ozonolysis afforded **4n** and **4o** in 87% and 88% yield, which were converted into the desired cyclopropanes **5n** in 80% yield and **5o** in 68% yield under the usual conditions. It is worth noting that both of these two reactions proceeded rapidly since the starting thiolcarbonates

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were totally consumed in 30 to 40 min. And, in both cases, a 1:1 ratio of epimers was observed (Scheme 3).

In summary, we have developed a convenient, practical, and convergent sequence to access cyclopropanes substituted with two electron-withdrawing groups. In particular, we were able to obtain silicon substituted derivatives. The silicon group can act in principle as a precursor of the corresponding iodide, which can then be subjected to various organometallic couplings.[18] Furthermore, as abundantly documented, the presence of the two electron-withdrawing groups activates the cyclopropane rings toward nucleophilic attack paving the way to numerous subsequent transformations.[19] Compared to more conventional methods, this approach avoids using expensive metal catalysts and ligands, as well as the use of potentially explosive and carcinogenic diazoalkanes. Further work is nevertheless still needed to expand the scope to aliphatic ketones.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.s.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated with respect to the memory of Prof. Ekkehard Winterfeldt (University of Hanover).

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