

## Addition-type Oxidation of Silylalkene Using Ozone: An Efficient Approach for Acyloin and Its Derivatives

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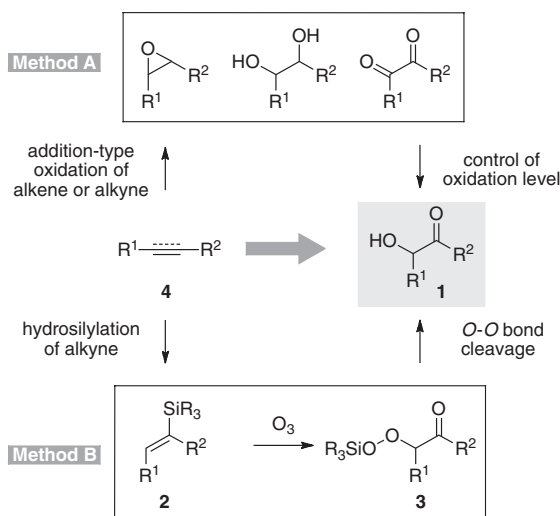
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Acyloins are efficiently synthesized in three steps from alkynes via hydrosilylation followed by an addition-type ozone oxidation and hydrogenation. The key intermediate  $\alpha$ -silylperoxy ketone is convertible to not only acyloin but also *O*-silylated acyloin and diketone.

Acyloins, namely  $\alpha$ -hydroxy ketones **1** are important as key structural components of biologically active natural products and as synthetic building blocks owing to their versatile bifunctionality.<sup>1,2</sup> Therefore, thus far, several synthetic approaches to acyloins have been developed. Among these approaches, acyloin condensation is one of the most widely used approaches, however, proper choice of substrate and harsh conditions are requisite for the reductive dimerization of esters.<sup>2a,2b</sup> As an alternative approach, a sequential method involving the oxidation of alkenes or alkynes and further transformation of the resulting oxy-functionalized intermediates such as epoxide, diol, or diketone is also commonly used.<sup>3</sup> However, in this method, it is rather complicated to control the oxidation level of vicinal carbons having the same oxy-functionality, which often leads to the formation of a regioisomer of acyloin (Scheme 1, Method A). To avoid these longstanding problems, a more efficient synthetic approach for acyloin is needed.

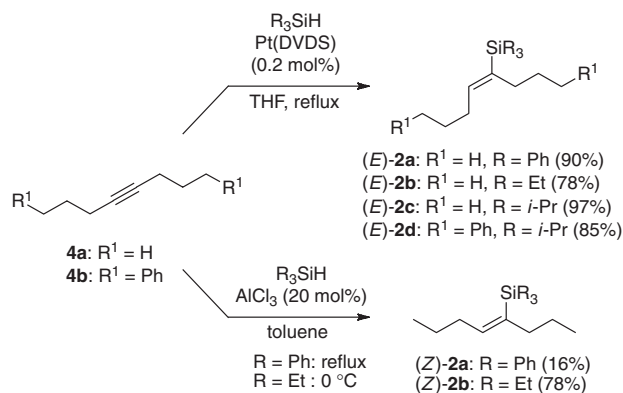


**Scheme 1.** Synthetic approach to acyloin based on oxidation of an unsaturated carbon-carbon bond.

To this end, we recently found that ozone oxidation of 1-silyl-substituted terminal alkenes **2** ( $R^2 = H$ ) affords  $\alpha$ -silylper-

oxy aldehydes **3** ( $R^2 = H$ ) introducing silylperoxy and carbonyl moieties on vicinal carbons without normal fission of the carbon-carbon double bond.<sup>4</sup> This result clearly suggests that a similar ozone oxidation of silyl-substituted internal alkene **2** ( $R^2 = \text{alkyl}$ ) should yield the corresponding  $\alpha$ -silylperoxy ketone **3** ( $R^2 = \text{alkyl}$ ), which has versatile functional groups for synthesis of a variety of oxy-functionalized compounds containing acyloin.<sup>5-8</sup> Herein, we report a new efficient synthetic approach for acyloins and their derivatives from alkynes **4** via sequential hydrosilylation followed by addition-type ozone oxidation (Scheme 1, Method B).<sup>9</sup>

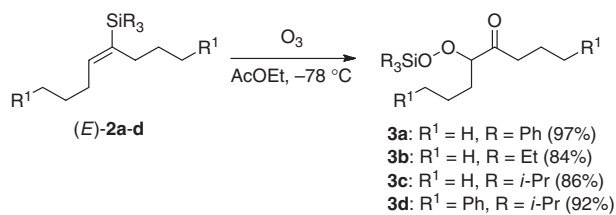
First, we performed (*E*)- or (*Z*)-selective hydrosilylation of 4-octyne (**4a**) and 1,8-diphenyl-4-octyne (**4b**) by previously reported procedures.<sup>10</sup> The hydrosilylation of **4a** and **4b** in the presence of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane [Pt(DVDS)] afforded (*E*)-**2a-2d** in good yields with excellent *E*-selectivities (>99% *E*).<sup>11</sup> On the other hand, Yamamoto and Asao's Lewis acid-promoted hydrosilylation of **4a** afforded (*Z*)-**2a** and **-2b** as the sole isomer (>99% *Z*) (Scheme 2).<sup>12</sup>



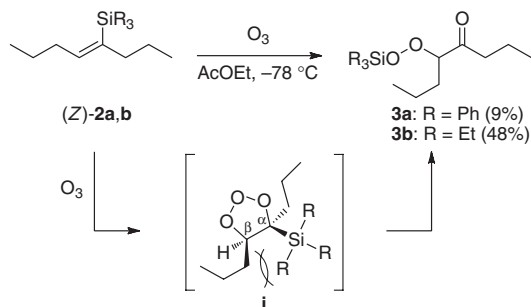
**Scheme 2.** Hydrosilylation of alkyne **4a** and **4b**.

Ozone oxidation of silylalkenes **2** was performed by bubbling ca. 1.2 v/v%  $O_3/O_2$  gas in AcOEt at  $-78^\circ C$ .<sup>13</sup> The reactions of (*E*)-**2a-2d** afforded the corresponding  $\alpha$ -silylperoxy ketones **3a-3d** in excellent yields, regardless of the different silyl groups [TPS ( $R = Ph$ ), TES ( $R = Et$ ), and TIPS ( $R = i\text{-Pr}$ )] (Scheme 3).<sup>14</sup>

In sharp contrast, a similar oxidation of (*Z*)-**2a** ( $R_3Si = \text{TPS}$ ) afforded **3a** in a very low yield (9%) (Scheme 4).<sup>15</sup> The remarkable difference between (*E*)-**2a** and (*Z*)-**2a** is probably due to the steric repulsion of the bulky silyl group with the  $\beta$ -*cis*-substituent in the silyl migration stage of primary ozonide **i**, as shown in Scheme 4. On the basis of this working hypothesis,



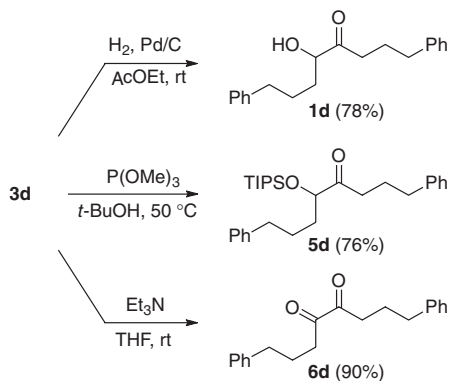
**Scheme 3.** Ozone oxidation of *(E)*-silylalkenes [(*E*)-**2a–2d**].



**Scheme 4.** Ozone oxidation of *(Z)*-silylalkenes [(*Z*)-**2a** and **-2b**].

we anticipated that a decrease in the bulkiness of the silyl group would improve the efficiency of the addition-type ozone oxidation of *(Z)*-**2**. As we expected, a similar reaction of *(Z)*-**2b** with a smaller silyl group ( $\text{R}_3\text{Si} = \text{TES}$ ) afforded **3b** in a considerably better yield (48%) than that of *(Z)*-**2a**.

The  $\alpha$ -silylperoxy ketones **3** thus obtained are easily and efficiently convertible into free or *O*-silylated acyloins. As shown in Scheme 5, hydrogenation of **3d** catalyzed by Pd/C afforded free acyloin **1d** in 78% yield by reductive *O–O* bond cleavage.<sup>8a</sup> To transform **3d** into *O*-silylated acyloin **5d**, we examined conventional methods for the reduction of the silyl peroxide moiety using  $\text{PPh}_3$  or  $\text{PMe}_3$ .<sup>4,8,16,17</sup> However, the reactions involved in these methods required a long time along with partial decomposition of **3d**. After several attempts, we found that the reaction of **3d** with  $\text{P}(\text{OMe})_3$  in *t*-BuOH smoothly afforded **5d** in good yield (76%). Furthermore, we successfully converted **3d** to 1,2-diketone **6d** in 90% yield by  $\text{Et}_3\text{N}$  treatment.



**Scheme 5.** Transformation of  $\alpha$ -silylperoxy ketone **3d**.

The above-mentioned synthetic approach for *O*-silylated acyloin is also applicable to a variety of functionalized alkynes.

**Table 1.** Synthesis of *O*-silylated acyloins **5e–5h** from alkyne **4e–4h**

Reaction scheme showing the synthesis of *O*-silylated acyloins **5e–h** from alkynes **4e–h**. The reaction sequence involves hydrosilylation of **4e–h** with TIPS-H and  $\text{Pt}(\text{DVDS})$  in neat conditions at  $80^\circ\text{C}$  to form **2e–h**, followed by ozone oxidation of **2e–h** in  $\text{AcOEt}$  at  $-78^\circ\text{C}$  to form **3e–h**, and finally phosphite reduction of **3e–h** with  $\text{P}(\text{OMe})_3$  in *t*-BuOH at  $50^\circ\text{C}$  to yield **5e–h**.

Entry	4	R	Yields of <b>2</b> <sup>a</sup> /%	Yields of <b>5</b> <sup>b</sup> /%
1	<b>4e</b>	TBS	75 ( <b>2e</b> ) (>99% <i>E</i> )	64 ( <b>5e</b> )
2	<b>4f</b>	Bn	95 ( <b>2f</b> ) ( <i>E/Z</i> = 95/5) <sup>c</sup>	57 ( <b>5f</b> )
3	<b>4g</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	99 ( <b>2g</b> ) ( <i>E/Z</i> = 89/11) <sup>c</sup>	45 ( <b>5g</b> )
4	<b>4h</b>	<i>p</i> -CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	94 ( <b>2h</b> ) ( <i>E/Z</i> = 85/15) <sup>c</sup>	53 ( <b>5h</b> )

<sup>a</sup>Isolated yields. <sup>b</sup>Isolated yields from **2**. <sup>c</sup>Determined by GLC analysis.

For example, the sequential reaction of the disilyl ether of 2-butyne-1,4-diol **4e** with hydrosilylation and ozone oxidation followed by phosphite reduction afforded *O*-silylated acyloin **5e** with oxy-functions on all the carbons, in good yield (Table 1, Entry 1).<sup>18</sup> Similar reactions of dibenzyl ether derivatives **4f–4h** also afforded *O*-silylated acyloins **5f–5h** in moderate yields, regardless of the functional groups on the aromatic ring (Table 1, Entries 2–4).<sup>19,20</sup> These results clearly show that the present sequential conversion of alkyne is an efficient approach for synthetically variable multifunctionalized acyloin derivatives.

In summary, we have described a new synthetic approach for acyloin and its derivatives using the addition-type ozone oxidation of silylalkene. In the described approach, easily available and chemically stable silylalkene moieties serve as synthetic equivalents of acyloin moieties. Further applications of the present synthetic method to natural product synthesis are in progress.

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- 20 Although, ozone is capable of oxidizing benzylic carbon, no such products were observed in the ozone oxidation of **2f–2h**.
- 21 Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.