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One-Pot γ-Lactonization of Homopropargyl Alcohols via Intramolecular Ketene Trapping

Daichi Yamane,[†] Haruna Tanaka,[†] Akihiro Hirata,[†] Yumiko Tamura, Daichi Takahashi, Yusuke Takahashi, Tohru Nagamitsu,* and Masaki Ohtawa*

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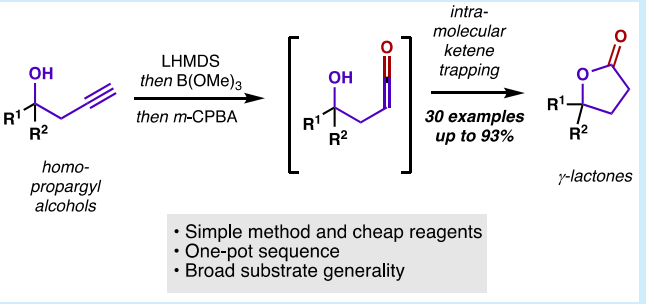
ABSTRACT: A one-pot γ-lactonization of homopropargyl alcohols via an alkyne deprotonation/boronation/oxidation sequence has been developed. Oxidation of the generated alkynyl boronate affords the corresponding ketene intermediate, which is trapped by the adjacent hydroxy group to furnish the γ-lactone. We have optimized the conditions as well as examined the substrate scope and synthetic applications of this efficient one-pot lactonization.



Five-membered cyclic esters, i.e., γ-lactones (γ-butyrolactones), are important bioactive molecules[1] and useful building blocks for various interesting target molecules.[2] γ-Lactones are often synthesized by intramolecular cyclizations of the corresponding hydroxycarboxylic acid (seco acid) or its esters;[3] however, functional group interconversions (FGIs) are needed to prepare these precursors. On the other hand, γ-lactonizations of homopropargyl alcohols involving stepwise and direct approaches have been developed (Figure 1). In the former case, γ-lactones are produced from lactols derived from homopropargyl alcohols[4] or the corresponding homoallyl alcohols[5] via hydroboration/oxidation followed by further oxidation of the lactols over multiple steps. The latter approaches are based on the intramolecular cyclization of alkyne-derived metal vinylidene intermediates. Dötz et al. have reported the first reaction of this type, in which isolable chromium vinylidene intermediates are formed from homopropargyl alcohols and subsequently oxidized with ceric ammonium nitrate (CAN) to afford γ-lactones.[6] After this report, several catalytic one-pot cyclizations of metal vinylidene intermediates (Ru cat.,[7] Au cat.[8]) have been reported. Although this approach can be carried out under mild conditions and exhibits a wide substrate generality, transition-metal catalysts which are not readily available are still required.

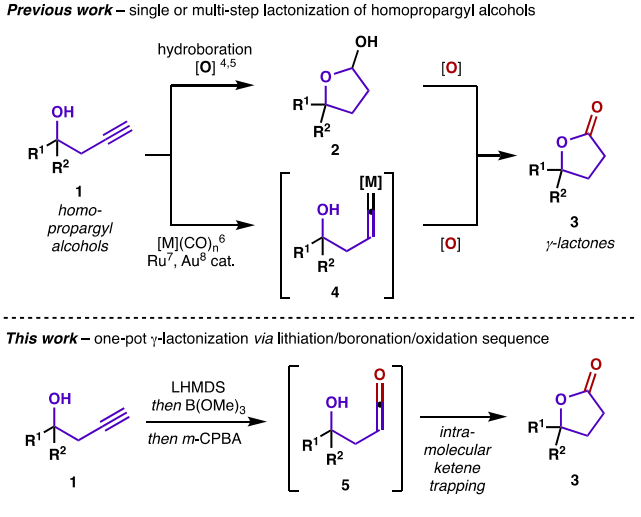


Figure 1. Previously reported lactonization strategies for propargyl alcohols and the approach used in this study.

In a previous study on the synthesis of (−)-bilobalide,[9] we have developed a novel γ-lactonization of homopropargyl alcohols (Figure 2). The construction of γ-lactone **7** from homopropargyl alcohol **6** was attempted using both stepwise (entries 1 and 2) and direct lactonization (entries 3[7] and 4[8a]) strategies; however, both approaches provided low or no yield of lactone **7**, most likely due to the steric hindrance. Next, we attempted the γ-lactonization of the ketene intermediate[10] generated from acetylide using the Li salt of *tert*-butyl hydroperoxide (TBHP),[11] but the oxidation did not proceed (entry 5). In another previous work, we have reported the

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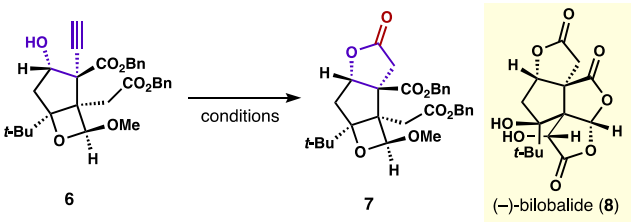


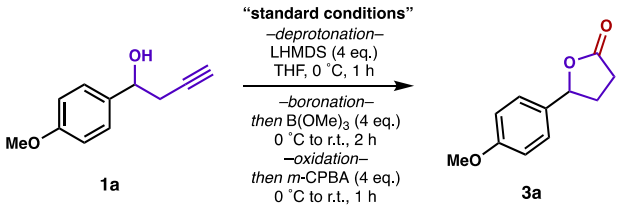
entry	conditions	product
1	1) Cy_2BH *then* $Na_2B_2O_8$ 2) TEMPO PIDA	<10% conversion
2	1) BH_3 THF *then* $Na_2B_2O_8$ 2) TEMPO, PIDA	23%
3	CpRuCl(bpy), PIDA	<5%
4	PPh_3AuNTf_2, *m*-CPBA	decomposition
5	LHMDS, LiOO*t*-Bu	N.R.
6	LHMDS *then* $B(OMe)_3$ *then* *m*-CPBA	55%

Figure 2. Discovery of new lactonization.

direct hydroxylation of pyridine via a lithiation/boronation ($B(OMe)_3$)/oxidation (*m*-chloroperoxybenzoic acid (*m*-CPBA)) sequence.[12] If this reaction could also be applied to the sp carbon, it would represent a new method of ketene generation via alkyne hydroxylation.[13] As expected, subjecting homopropargyl alcohol **6** to these conditions gave lactone **7** as the exclusive product in 55% yield (entry 6).

Nevertheless, this lactonization procedure uses common and inexpensive reagents and an easy one-pot sequence.[14] Therefore, it represents a new and useful alternative procedure to obtain γ-lactones from various homopropargyl alcohols. Our optimized conditions and instructive deviations are shown in Figure 3.

γ-Lactonization of **1a** under the "standard conditions" gave the desired product **3a** in 79% yield, accompanied by a small amount of the starting material **1a** (entry 1), and a scale-up of this reaction (entry 2) is easily possible. The optimum time and temperature for the boronation with $B(OMe)_3$ were determined to be 2 h at 0 °C (entries 3–5). The oxidation of the alkynyl boronate intermediate at low temperature (−78 °C) provided **3a** in 28% yield, together with a large amount of unreacted alcohol **1a** (entry 6). Variation of the reagents used in the deprotonation and boronation steps indicated that more basic (not nucleophilic) and less bulky reagents were most suitable for this conversion (entries 7 and 8). Next, various oxidants were examined. Neutral and basic oxidants, such as TBHP (entry 9) or *t*-BuOOLi[11] (entry 10), did not provide the desired lactone **3a**. When the slightly acidic oxidants triazox[15] and Oxone were used, lactone **3a** was obtained in 21% and 44% yield, respectively, although some uncharacterized byproducts were generated (entries 11 and 12). At this point, we focused on the recovered alcohol **1a** from each trial due to the stability of the alkynyl boronate intermediate. Brown has reported that the protonation of alkynyl boronate occurs easily in the presence of proton sources such as alcohols, water, and acids.[16] Commercially available *m*-CPBA contains 30–40% water and 4–5% *m*-chlorobenzoic acid (*m*-CBA) as stabilizers; therefore, anhydrous *m*-CPBA and purified *m*-CPBA[17] were prepared and used for the lactonization, but the results remained unchanged (entries 12 and 13). This result indicates that *m*-CPBA and *m*-CBA promote the generation and protonation of the alkynyl boronate intermediate. A more detailed discussion of the proposed reaction mechanism is presented later in the



entry	variations from "standard conditions"[a]	result 3a	result 1a
1[b]	none	**79%**	13%
2[b]	none (4.9 mmol scale)	**77%**	6%
3[b]	0 °C, 1 h (*boronation*)	25%	41%
4[b]	0 °C to r.t., 1 h (*boronation*)	52%	44%
5[b]	0 °C to r.t., 3 h (*boronation*)	49%	11%
6[b]	–78 °C to 0 °C, 2 h (*oxidation*)	28%	71%
7[b]	*n*-BuLi instead of LHMDS	21%	66%
8[b]	$B(Oi\text{-}Pr)_3$ instead of $B(OMe)_3$	50%	29%
9	TBHP instead of *m*-CPBA	0%	78%
10[c]	*t*-BuOOLi instead of *m*-CPBA	0%	62%
11[d]	Triazox[15] instead of *m*-CPBA	21%	15%
12[e]	Oxone instead of *m*-CPBA	44%	25%
13[f]	anhydrous *m*-CPBA instead of normal *m*-CPBA	57%	30%
14[g]	purified *m*-CPBA[17] (>95% purity) instead of normal *m*-CPBA	44%	14%
15[b]	3 eq. each reagent	**83%**	12%
16[b]	2.5 eq. each reagent	46%	51%

[a] 0.1 mmol scale.
[b] The purity of *m*-CPBA was >65%, also contained *m*-Cl benzoic acid and H_2O.
[c] *t*-BuOOLi was prepared from TBHP and LHMDS at 0 °C. The conditions of oxidation step were 0 °C to r.t.,18 h.
[d] The conditions of oxidation step were 0 °C to r.t., 18 h.
[e] A prepared saturated aqueous Oxone solution was used.
[f] A prepared CH_2Cl_2 solution of anhydrous *m*-CPBA was used.
[g] Prepared purified *m*-CPBA[17] was used.

Figure 3. Optimization of the reaction conditions.

manuscript (Figure 5). The influence of the number of equivalents of the reagents (lithium bis(trimethylsilyl)amide (LHMDS)/$B(OMe)_3$ and *m*-CPBA) was examined, and we found that the yield was maintained even when the amounts of both reagents were reduced to three equivalents (entries 14 and 15).

The optimized conditions were found to be applicable to the synthesis of γ-lactones from a wide range of homopropargyl alcohol substrates (Figure 4). Methoxy-, methyl-, chlorine-, bromine-, cyano-, and substituted phenyl groups were tolerated, regardless of the substitution position (**3a–m**); however, due to the rapid oxidation of the amino group, lactone **3l** could not be obtained. Synthesis of the monosubstituted γ-lactones **3n–s** including heteroaromatic rings was successfully achieved. Various disubstituted γ-lactones were also obtained in moderate yield (**3t–ab**). Notably, this reaction can also be applied to substrates with unsaturated bonds, which indicates that the oxidation of the alkynylboronate intermediates by *m*-CPBA is faster than the oxidation of unsaturated bonds.

Then, we applied this reaction to the relatively short synthesis of spironolactone (Scheme 1). Spironolactone has been semisynthesized from steroidal precursors using a variety of industrial methods; in the context of our study, the Ciba-

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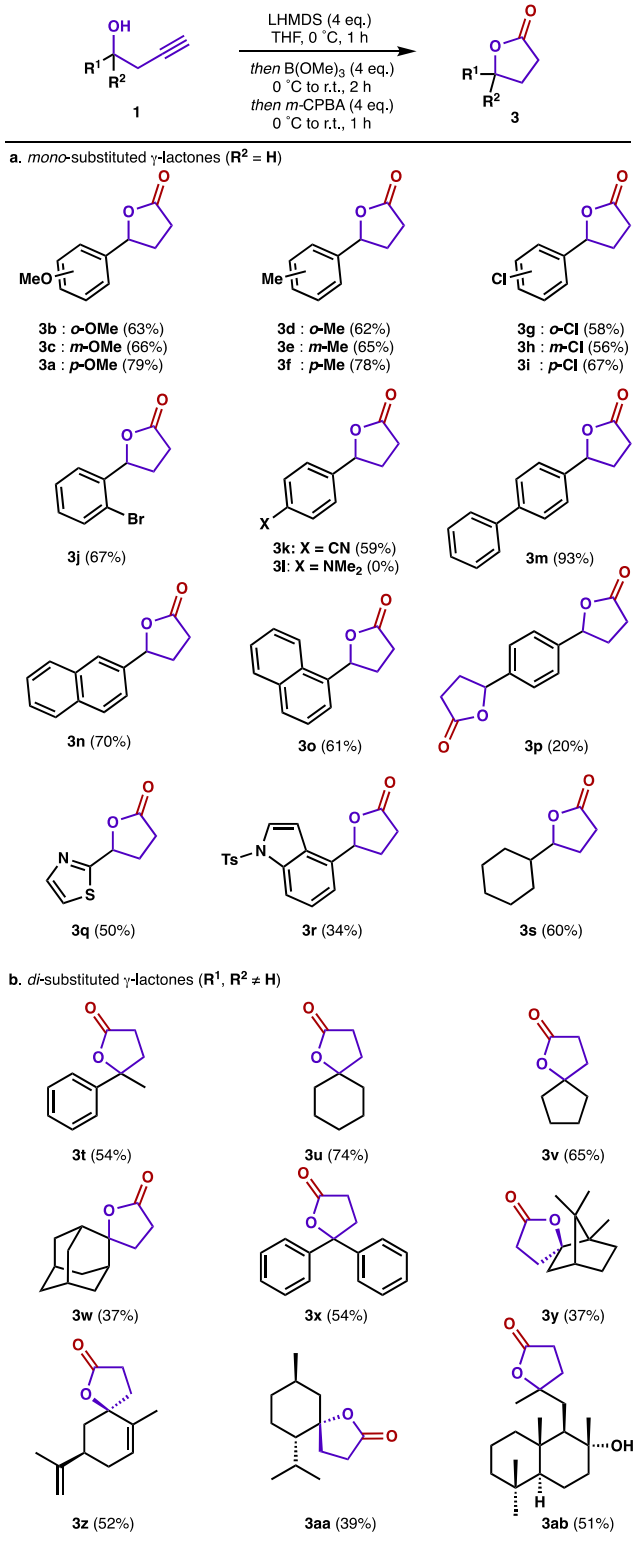
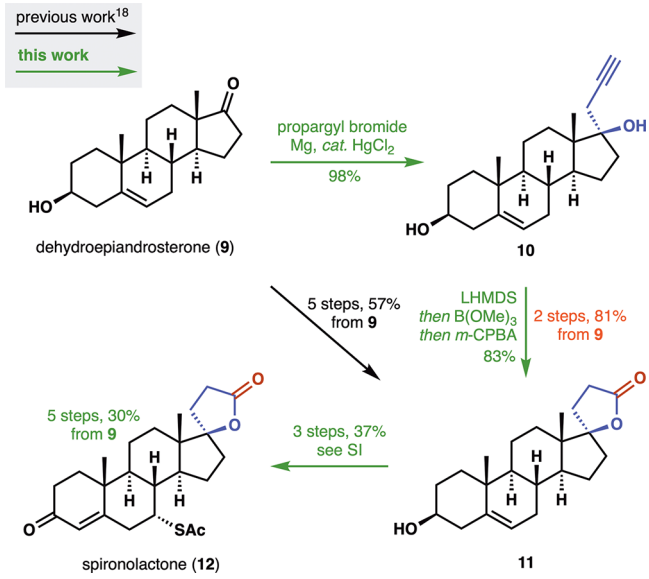


Figure 4. Substrate scope.

Geigy method should be mentioned, as it constructs γ-lactone **11** from dehydroepiendrosterone (**9**) in 5 steps, followed by 3 steps to produce spironolactone (**12**) industrially.[18] Subsequently, we applied our new lactonization method in an attempt to improve the synthesis of **12**. The homopropargyl intermediate **10** was obtained in 85% yield by treating dehydroepiendrosterone (**9**) with an *in situ*-prepared propargyl Grignard reagent in the presence of mercury(II) chloride. The

Scheme 1. Application to the Short Synthesis of Spironolactone (12)



following lactonization gave the Ciba-Geigy γ-lactone **11** intermediate in 83% yield in two steps from dehydroepiendrosterone (**9**) without compromising the unsaturated bonds. γ-Lactone **11** was subjected a sequential oxidation followed by the conjugate addition of thioacetic acid to afford spironolactone (**12**) (for details, see the SI). Thus, the present lactonization represents a short synthetic route (5 steps) from dehydroepiendrosterone (**9**) to spironolactone (**12**), showing that this method can be applied to the synthesis of various drugs and natural products containing γ-lactones.

A plausible mechanism of this reaction is shown in Figure 5. The starting material, homopropargyl alcohol **1**, is deprotonated by LHMDS to afford dilithium species **13**. Next, $B(OMe)_3$ is applied to form borate intermediate **14**, and the subsequent addition of *m*-CPBA or its contaminant *m*-CBA

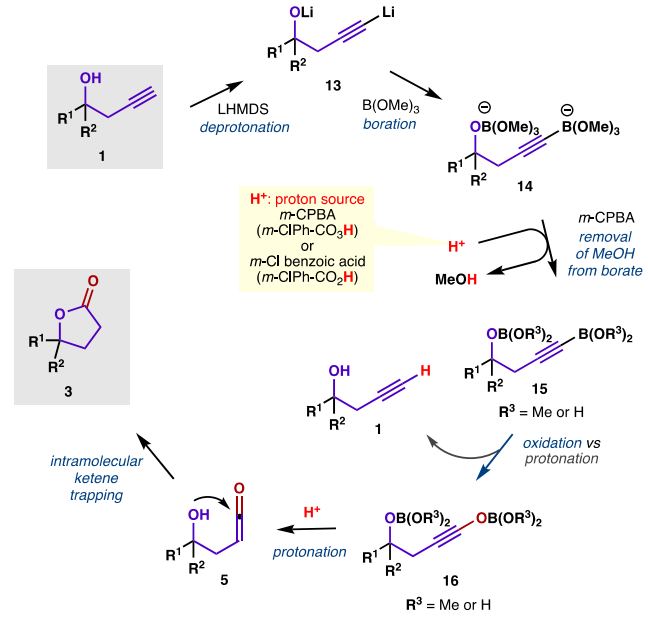


Figure 5. Plausible mechanism of the reaction.

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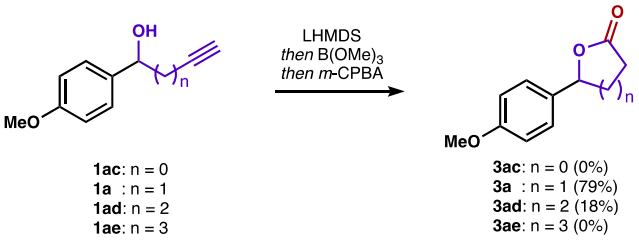
promotes the dissociation of MeOH from the borate to give alkynyl boronate or alkynyl boronic acid **15**. The oxidation of **14** does not proceed when TBHP or *t*-BuOOLi is used as the oxidant (Figure 3, entries 8 and 9); therefore, the presence of an acid to dissociate one MeOH from alkynyl boronate seems to be essential for this reaction. The resulting intermediate **15** is rapidly oxidized by *m*-CPBA to form ynol boronate or boronic acid **16**, and the intramolecular cyclization of the adjacent hydroxyl group to the protonated ketene intermediate **5** gives the corresponding lactone **3**.[19] One problem in this reaction is the potentially fast protonation of **15** to give starting material **1**. The protonation of **15** depends on the pK_a of the proton source;[16] however, it should be difficult to completely suppress the protonation due to the requirement of a proton (or Lewis acid) for the desorption of one molecule of MeOH from the alkynylborate intermediate *in situ*. Despite this limitation, this approach is a useful and simple functional-group-conversion method for the lactonization of homopropargylic alcohols in one pot with readily available reagents.

Finally, we applied this lactonization strategy to the synthesis of 4-, 6-, and 7-membered lactones (Scheme 2). However, we

Scheme 2. Attempted Lactonization of Various Alkynyl Alcohols



found that only the 6-membered ring lactone **3ad** was obtained from **1ad** in moderate yield. The reactions of **1ac** and **1ae** did not produce the corresponding lactones **3ac** and **3ae** and instead furnished complex mixtures including trace amounts of methyl esters due to the intermolecular esterification of the MeOH resulting from $B(OMe)_3$ and the corresponding carboxylic acid from the ketene intermediate due to the presence of water as a contaminant of *m*-CPBA. This result indicates that (i) the intermediate ketene is highly reactive and effective for the lactonization of more suitable substrates (e.g., γ-lactone precursors), and (ii) it could also be extended to intermolecular reactions to give carboxylic acids, esters, or amides in the presence of appropriate acceptors.

In summary, we have reported a useful method for the lactonization of homopropargyl alcohols via a ketene intermediate. In this one-pot reaction, which involves a deprotonation, boronation, and oxidation of a terminal alkyne, the corresponding γ-lactones are obtained via the intramolecular cyclization of the ketene intermediates. This simple transformation thus represents a useful method for the oxidation of alkynes that does not require the isolation of intermediates and can be achieved using commercially available and inexpensive reagents. This γ-lactonization exhibits a broad substrate generality and is not only applicable to various homopropargyl alcohols but also effective for the short synthesis of pharmaceuticals such as a spironolactone. The application of this method to intramolecular lactams and intermolecular reactions is currently in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00840.

Experimental procedures and spectroscopic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Masaki Ohtawa − *Laboratory of Synthetic Natural Products Chemistry and Medicinal Research Laboratories, School of Pharmacy, Kitasato University, Minato-ku, Tokyo 108-8641, Japan*; orcid.org/0000-0001-7129-012X; Email: ohtawam@pharm.kitasato-u.ac.jp

Tohru Nagamitsu − *Laboratory of Synthetic Natural Products Chemistry and Medicinal Research Laboratories, School of Pharmacy, Kitasato University, Minato-ku, Tokyo 108-8641, Japan*; orcid.org/0000-0002-4278-4507; Email: nagamitsut@pharm.kitasato-u.ac.jp

Authors

Daichi Yamane − *Laboratory of Synthetic Natural Products Chemistry and Medicinal Research Laboratories, School of Pharmacy, Kitasato University, Minato-ku, Tokyo 108-8641, Japan*

Haruna Tanaka − *Laboratory of Synthetic Natural Products Chemistry and Medicinal Research Laboratories, School of Pharmacy, Kitasato University, Minato-ku, Tokyo 108-8641, Japan*

Akihiro Hirata − *Laboratory of Synthetic Natural Products Chemistry and Medicinal Research Laboratories, School of Pharmacy, Kitasato University, Minato-ku, Tokyo 108-8641, Japan*

Yumiko Tamura − *Laboratory of Synthetic Natural Products Chemistry and Medicinal Research Laboratories, School of Pharmacy, Kitasato University, Minato-ku, Tokyo 108-8641, Japan*

Daichi Takahashi − *Laboratory of Synthetic Natural Products Chemistry and Medicinal Research Laboratories, School of Pharmacy, Kitasato University, Minato-ku, Tokyo 108-8641, Japan*

Yusuke Takahashi − *Laboratory of Synthetic Natural Products Chemistry and Medicinal Research Laboratories, School of Pharmacy, Kitasato University, Minato-ku, Tokyo 108-8641, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00840

Author Contributions

†D.Y., H.T., and A.H. contributed equally.

Notes

The authors declare no competing financial interest.

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discovering the lactonization in the synthetic study on bilobalide.[9]

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(19) γ-Lactonization of TBS-protected **1a** did not provide lactone **3a**. This result indicates that the free hydroxyl group is necessary for the cyclization of the resulting ketene intermediate.

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