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Lewis acid-catalyzed intramolecular condensation of ynol ether-acetals. Synthesis of alkoxy cycloalkene carboxylates

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Abstract

Treatment of ynol ether-tethered dialkyl acetals with catalytic quantities of scandium triflate in CH_3CN gives rise to five-, six-, and seven-membered alkoxy cycloalkene carboxylates in good to excellent yields. Trisubstituted and tetrasubstituted carbocyclic and heterocyclic alkenes may be formed by this method, and the products obtained may serve as useful intermediates for natural product synthesis.

Alkoxy cycloalkene carboxylates are highly useful starting materials for organic synthesis (Figure 1). Stereoselective introduction of carbon substituents β to the ester functional group may be accomplished by allylic substitution or Michael addition reactions, as shown by Villieras et al.¹ Ogasawara has prepared the nitraria alkaloids (+)-nitramine, (+)-isonitramine, and (–) sibirine from 2-carboethoxy-2-cyclohexen-1-ol.² Similarly, Iwabuchi's recent synthesis of idesolide commences from 2-carbomethoxy-2-cyclohexen-1-ol.³ Lupton has also accomplished an elegant total synthesis of 7-deoxyloganin from 2-carboethoxy-2-cyclopenten-1-ol.⁴ In all cases, the hydroxycycloalkene carboxylate starting material is prepared in moderate yields by the Horner-Wadsworth-Emmons reaction of an appropriate dialdehyde with trialkyl phosphonacetate.⁵ Since the efficiency of this protocol is often low, the development of an alternative method for the preparation of cycloalkenol carboxylates of varying ring sizes would clearly be of value for natural product synthesis. In this Letter we report our efforts toward the realization of this goal and detail a novel Lewis acid-catalyzed condensation of ynol ether-acetals that yields alkoxy cycloalkene carboxylates in high yields.

Electron-rich alkynes, such as ynamines and ynol ethers, are functional groups that possess significant potential in organic chemistry for the formation of carbon-carbon bonds.⁶ Due to their linear geometry, alkynyl ethers are relatively unhindered to approach by functional groups present in the same or different molecules; furthermore, alkynyl ethers can prospectively form up to three new bonds in a single reaction (Figure 2).

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Supporting Information Available Experimental details, characterization data, ^1H , ^{13}C spectra of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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We have recently shown that *tert*-butyl ynol ethers bearing tethered alkenes form substituted cyclobutanones in high yields under mild thermal conditions.^{7a} In attempting to extend this method to the preparation of β -lactones and lactams through thermolysis of ketone and aldehyde-tethered ynol ethers, we discovered that attempted deprotection of the acetal precursors led to the formation not of the desired carbonyl-containing ynol ethers, but rather of alkoxy cycloalkene carboxylates (Scheme 1). Thus, treatment of acetal **2aa** (prepared from aldehyde **1a** by addition of *tert*-butoxyethynyllithium^{7b} and silyl protection of the resulting propargylic alcohol) with 5 mol % I_2 in acetone⁸ at room temperature for five minutes gave rise to silyloxycycloalkene carboxylate **3aa** in 45% yield, as well as a 1:1 mixture of the more polar methyl esters **3ab** and **3ac** in 40% yield. Interestingly, treatment of ethyl alkynyl ether **2ab** with $Sc(OTf)_3$ in CH_3CN led to the formation of ethyl ester **3ad** cleanly in 80% yield; however, addition of up to 15 mol % of catalyst was necessary in order to achieve optimal conversion of **2ab** to **3ad**. On large scale (>500 mg), the increased amounts of Lewis acid catalyst required led to side products arising from cleavage of the silyl ether protecting group and lower (60–70%) yields of **3ad**.

These initial results prompted us to evaluate the use of other Lewis acids to catalyze the apparent cyclocondensation process (Table 1). Addition of $Sc(OTf)_3$ (5 mol %) to substrate **2aa** in CH_3CN gave a 78% yield of **3aa** within 5 minutes at room temperature with only trace amounts of **3ab** and **3ac** formed. $In(OTf)_3$ ^{9a} and $Zn(OTf)_2$ also provided **3aa**, although in significantly lower yields (50% and 25%, respectively); moreover, complete consumption of **2a** was never achieved, even with the addition of excess catalyst (up to 15 mol %) to the reaction mixture.

Treatment of **2aa** with the Lewis acids $AgOTf$ or $BiCl_3$ ^{9b} in CH_3CN led to significant amounts of substrate decomposition, with only minute quantities (<5%) of **3aa** recovered from the reaction mixtures. In contrast, no reaction occurred when **2aa** was stirred in the presence of $InCl_3$, even after one hour. Finally, treatment of **2a** with 5 mol % $TMSOTf$ in CH_2Cl_2 at $-78^\circ C$ gave **3aa** in 70% yield after silica gel chromatography.

A possible mechanistic pathway for this process (Scheme 2) might involve Lewis-acid coordination of the acetal oxygen atom, followed by ionization and [2+2] cycloaddition. Loss of isobutylene accompanied by ring opening would then furnish either unsaturated methyl ester **3aa** or ketene **A**. Methanol trap of **A** would provide **3ac**; Lewis-acid mediated allylic substitution of **3aa** with the liberated methanol molecule could give rise to **3ab**. Ester **3ac** does not convert into **3aa** upon prolonged exposure to Lewis acid; however, extended reaction times and/or the addition of excess Lewis acid results in the conversion of unsaturated ester **3aa** into methyl ether **3ab**. A similar pathway from **2ab** to **3ad** could proceed through S_N2 -like cleavage of the oxonium methyl group, followed by pericyclic ring opening of the oxetene intermediate (Scheme 3).¹⁰

To explore the scope of this process, substrates **2b–2g** (Table 2) were prepared in a similar fashion (see Supporting Information)¹² and treated with catalytic amounts of Lewis acid at room temperature or $-78^\circ C$. While scandium triflate was an effective Lewis acid for ketone-derived acetals, $TMSOTf$ proved to be similarly efficient for aldehyde derived acetals. Five- (entries 1–4) and six- (entries 5–7) membered rings may be prepared in good to excellent yields in this manner. Furthermore, both trisubstituted (entries 3 and 7) and tetrasubstituted (entries 1, 2 and 4–6) cycloalkenes are formed with similar efficiencies. Silyl protecting groups employed in cyclization substrates **2** include TBS (entry 2) and TBDPS (*tert*-butyldiphenylsilyl, entries 1 and 3–7) and are necessary to avoid the facile Meyer-Schuster rearrangement¹¹ that is observed for the corresponding propargylic alcohols under Lewis acidic reaction conditions. It was subsequently discovered (Table 3, entry 2)

that protection of tertiary propargylic alcohols as their methyl ethers was also suitable for the cyclocondensation process (*vide infra*).

Extension of this chemistry to the synthesis of seven-membered alkoxy-cycloalkene carboxylates was also possible. While substrate **2h** disappointingly gave only a 5:1 mixture of acyclic ketoester **4** and unsaturated ester **5** upon exposure to catalytic quantities of scandium triflate, under the same conditions diethylacetal **2i** gave a 72% yield of the expected ethyl ester **3i** (Scheme 4). From these data it appears that substrate preorganization to allow proximity of the ynol ether and acetal termini is important for successful application of this method to the synthesis of medium-ring containing products. Table 3 shows several additional examples of the preparation of trisubstituted (entries 1–3, 5) and tetrasubstituted (entry 4) cycloalkenes containing 5–7 and 6–7 ring systems utilizing this methodology. Seven-membered cyclic ethers such as **3j** may be prepared containing a tertiary methyl ether (entry 2). Moreover, fused 5–7 ring systems similar to that found in guaiane-type sesquiterpene natural products (**m**, entry 5) could also be synthesized in moderate yields. Compounds **2k–2m** and **3k–3m** were obtained as a mixture of diastereomers (2:1 for **2k**, **2l**, **3k**, and **3l**, and 3:1 for **2m** and **3m**) resulting from the low stereoselectivity of the addition of (ethoxyethynyl)lithium to the corresponding aldehyde precursors.

In summary, we have shown that acetal-tethered alkynyl ethers undergo facile intramolecular condensation reactions under Lewis acid catalysis to form 5, 6, and 7-membered alkoxy-cycloalkene carboxylates, compounds which are useful intermediates for natural product synthesis. We are currently exploring methods for the preparation of optically-enriched cycloalkene carboxylates from the asymmetric addition of alkynyl ether anions to aldehyde and ketones, and the results of this study will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The utility of alkoxy cycloalkene carboxylates in natural product synthesis.

Figure 2.

The reactivity of 1-alkynyl ethers and their transformation to cyclobutanones

Scheme 1.
Attempted deprotection of dimethyl acetals **2aa**, **2ab**

Scheme 2.
Possible mechanism for formation of **3aa-3ac**.

Scheme 3.
Possible mechanism for formation of **3ad**

Scheme 4.
Requirements for seven-membered ring formation

Table 1Screen of Lewis acid catalysts for the transformation of **2aa** to **3aa**.^a

entry	catalyst	solvent	time (min)	% yield 3aa ^b
1	I ₂	acetone	5	45
2	Sc(OTf) ₃	CH ₃ CN	5	78
3	In(OTf) ₃	CH ₃ CN	10	50
4	Zn(OTf) ₂	CH ₃ CN	10	25
5	AgOTf	CH ₃ CN	10	<5 ^c
6	BiCl ₃	CH ₃ CN	10	<5 ^c
7	InCl ₃	CH ₃ CN	60	nr
8	TMSOTf ^d	CH ₂ Cl ₂	10	70

^a All reactions were performed with 5 mol % catalyst in solvent (0.15 M) at room temperature before quenching with saturated NaHCO₃ solution.^b Isolated yield after silica gel chromatography.^c Substrate decomposition occurred.^d Reaction performed at −78 °C for 10 min.

Table 2

Scope of Lewis-acid catalyzed intramolecular cyclocondensation, **2**→**3**.^a

entry	2	3	conditions ^b	% yield ^c
1	2a	3a	A	78
2	2b	3b	B	68
3	2c	3c	C	57
4	2d	3d	A	82
5	2e	3e	A	92
6	2f	3f	A	55
7	2g	3g	A	50

^aR¹=*tert*-butyldiphenylsilyl; R²=*tert*-butyldimethylsilyl.^bConditions: A, Sc(OTf)₃ (5 mol %), CH₃CN, rt, 10 min; B, I₂ (5 mol %), acetone, rt, 5 min; C, TMSOTf (5 mol %), CH₂Cl₂, −78 °C, 10 min.^cIsolated yield after column chromatography.

Table 3

Preparation of seven-membered cycloalkenes^a

entry	2^b	3	yield ^c
1	2i	3i	72
2	2j	3j	61
3	2k	3k	68 ^d
4	2l	3l	55 ^d
5	2m	3m	49 ^e

^aReaction conditions: 0.33 M **2** in CH₃CN, Sc(OTf)₃ (10 mol %), rt, 10 minutes.^bFor preparation of **2i-2m**, see Supporting Information and references 13–17.^cIsolated yield after column chromatography^dCompounds **2k**, **2l**, **3k**, and **3l** are composed of a 2:1 mixture of diastereomers. See text and references 15 and 16.^eCompounds **2m** and **3m** are composed of a 3:1 mixture of diastereomers. See text and reference 17.