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Lewis Acid Catalyzed Intramolecular Condensation of Ynol Ether-Acetals. Synthesis of Alkoxycycloalkene Carboxylates

Vincent Tran and Thomas G. Minehan*

Department of Chemistry and Biochemistry, California State University, Northridge 18111 Nordhoff Street, Northridge, California 91330, United States

thomas.minehan@csun.edu

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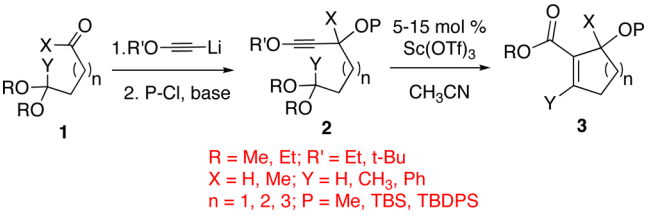
ABSTRACT



Treatment of ynol ether-tethered dialkyl acetals with catalytic quantities of scandium triflate in CH_3CN gives rise to five-, six-, and seven-membered alkoxycycloalkene carboxylates in good to excellent yields. Tri- 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.

Alkoxycycloalkene 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. Here we report our efforts toward the realization of this goal and detail a novel Lewis acid catalyzed condensation of ynol ether-acetals that yields alkoxycycloalkene 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 C−C bonds.[6] Due to their linear geometry, alkynyl ethers are relatively unhindered

(1) (a) Dambrin, V.; Villieras, M.; Janvier, P.; Toupet, L.; Amri, H.; Lebreton, J.; Villieras, J. *Tetrahedron* **2001**, *57*, 2155. (b) Amri, H.; Villieras, J. *Tetrahedron Lett*. **1987**, *28*, 5521. (c) Amri, H.; Rambaud, M.; Villieras, J. *Tetrahedron* **1990**, *46*, 3535. (d) Amri, H.; Rambaud, M.; Villieras, J. *J. Organomet. Chem*. **1986**, *308*, C27. (e) Dambrin, V.; Villieras, M.; Moreau, C.; Amri, H.; Toupet, L.; Villieras, J. *Tetrahedron Lett*. **1996**, *37*, 6323.

(2) Yamane, T.; Ogasawara, K. *Synlett* **1996**, 925.

(3) Yamakoshi, H.; Shibuya, M.; Tomizawa, M.; Osada, Y.; Kanoh, N.; Iwabuchi, Y. *Org. Lett*. **2010**, *12*, 980.

(4) Candish, L.; Lupton, D. W. *Org. Lett*. **2010**, *12*, 4836.

(5) (a) Brady, W. T.; Giang, Y. F. *J. Org. Chem*. **1985**, *50*, 5177. (b) Graff, M.; Al Dilaimi, A.; Seguineau, P.; Rambaud, M.; Villieras, J. *Tetrahedron Lett*. **1986**, *27*, 1577.

(6) For reviews of the chemistry of ynol ethers and the methods for the synthesis of ynol ethers, see: (a) Brandsma, L.; Bos, H. J.; Arens, J. F. In *The Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969, pp 751−860. (b) Stang, P. J.; Zhdankin, V. V. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons: New York, 1994; Chapter 19. For a review of the chemistry of ynamines and ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, H.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev*. **2010**, *110*, 5064–5106. (b) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. L. *Tetrahedron* **2001**, *57*, 7575–7606. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, *10*, 1379–1390. (c) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett*. **2008**, *10*, 661.

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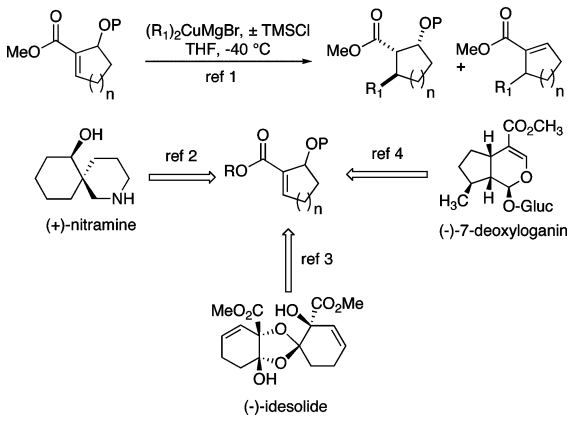


Figure 1. Utility of alkoxycycloalkene carboxylates in natural product synthesis.

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).

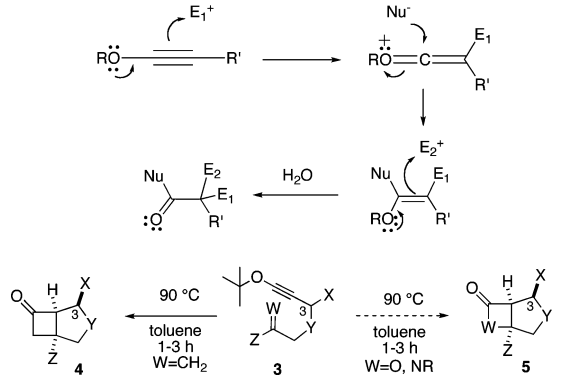
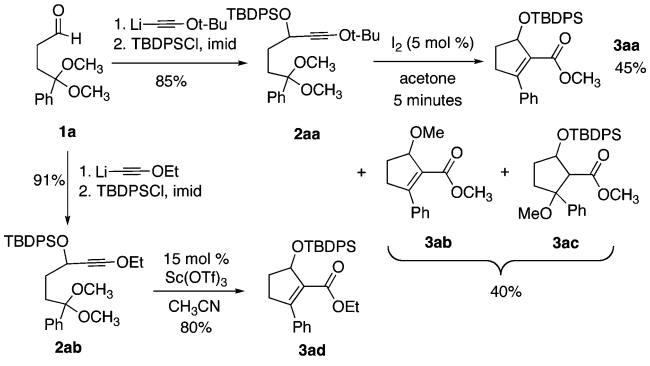


Figure 2. Reactivity of 1-alkynyl ethers and their transformation to cyclobutanones.

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 of alkoxycycloalkene carboxylates rather than the desired carbonyl-containing ynol ethers (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 acetone[8] at rt for 5 min gave rise to silyloxycycloalkene carboxyate **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 min 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.

Scheme 1. Attempted Deprotection of Dimethyl Acetals **2aa**, **2ab**



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 1 h. Finally, treatment of **2a** with 5 mol % TMSOTf in CH_2Cl_2 at −78 °C gave **3aa** in 70% yield after silica gel chromatography.

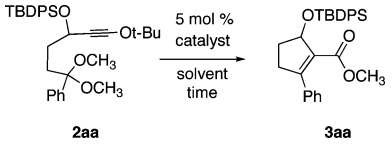
A possible mechanistic pathway for this process (Scheme 2) might involve Lewis acid coordination of the acetal oxygen atom, followed by ionization and [2 + 2] cycloaddition. Loss of isobutylene accompanied by ring opening would then furnish either unsaturated methyl ester **3aa** or ketene **A**. A methanol trap of **A** would provide **3ac**; Lewis acid

(7) (a) Tran, V.; Minehan, T. G. *Org. Lett.* **2011**, *13*, 6588. (b) *tert*-Butoxyethynyllithium was prepared from 1,2-dichlorovinyl *tert*-butyl ether by the protocol of Danheiser: Mak, X. Y.; Ciccolini, R. P.; Robinson, J. M.; Tester, J. W.; Danheiser, R. L. *J. Org. Chem.* **2009**, *74*, 9381.

(8) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932.

(9) (a) Gregg, B. T.; Golden, K. C.; Quinn, J. F. *J. Org. Chem.* **2007**, *72*, 5890. (b) Swamy, N. R.; Venkateswarlu, Y. *Tetrahedron Lett.* **2002**, *43*, 7549.

Table 1. Screen of Lewis Acid Catalysts for the Transformation of **2aa** to **3aa**[a]

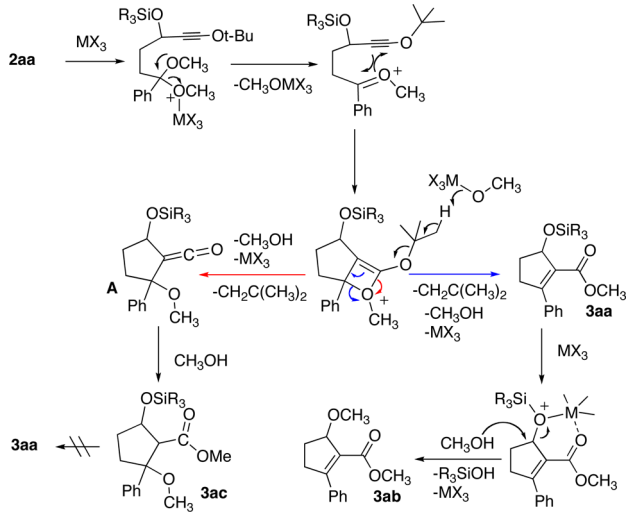


entry	catalyst	solvent	time (min)	% yield **3aa**[b]
1	I_2	acetone	5	45
2	**$Sc(OTf)_3$**	**CH_3CN**	**5**	**78**
3	$In(OTf)_3$	CH_3CN	10	50
4	$Zn(OTf)_2$	CH_3CN	10	25
5	AgOTf	CH_3CN	10	<5[c]
6	$BiCl_3$	CH_3CN	10	<5[c]
7	$InCl_3$	CH_3CN	60	nr
8	TMSOTf[d]	CH_2Cl_2	10	70

[a] All reactions were performed with 5 mol % catalyst in solvent (0.15 M) at rt before quenching with saturated $NaHCO_3$ solution. [b] Isolated yield after silica gel chromatography. [c] Substrate decomposition occurred. [d] Reaction performed at −78 °C for 10 min.

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]

Scheme 2. Possible Mechanism for Formation of **3aa**−**3ac**



(10) (a) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231. (b) Shindo, M.; Mori, S. *Synlett* **2008**, 2231. (c) Yoshikawa, T.; Shindo, M. *Org. Lett.* **2009**, *11*, 5378.

Scheme 3. Possible Mechanism for Formation of **3ad**

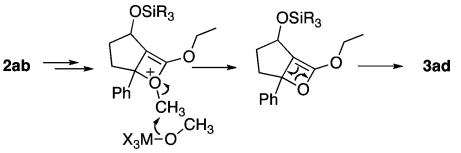
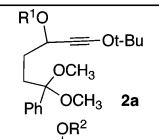
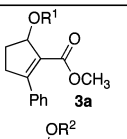
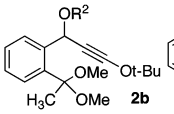
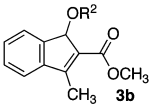
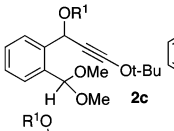
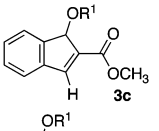
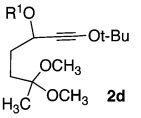
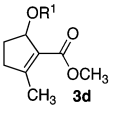
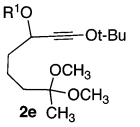
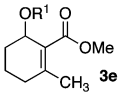
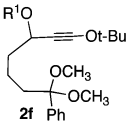
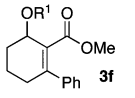
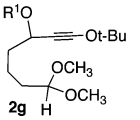
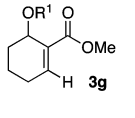


Table 2. Scope of Lewis Acid Catalyzed Intramolecular Cyclocondensation, **2**→**3**[a]

entry	**2**	**3**	conditions[b]	% yield[c] **3**
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

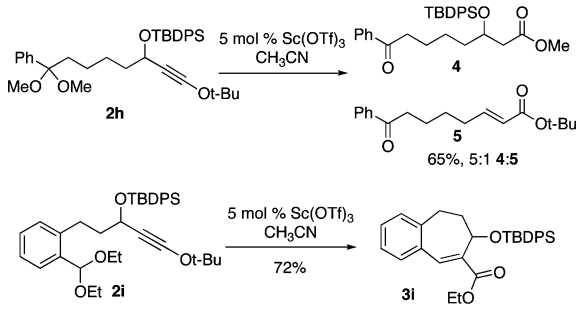
[a] R^1 = *tert*-butyldiphenylsilyl; R^2 = *tert*-butyldimethylsilyl. [b] Conditions: (A) $Sc(OTf)_3$ (5 mol %), CH_3CN, rt, 10 min; (B) I_2 (5 mol %), acetone, rt, 5 min; (C) TMSOTf (5 mol %), CH_2Cl_2, −78 °C, 10 min. [c] Isolated yield after column chromatography.

To explore the scope of this process, substrates **2b**−**2g** (Table 2) were prepared in a similar fashion (see Supporting Information (SI))[12] and treated with catalytic amounts of a Lewis acid at rt or −78 °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)

(11) For a recent review of the Meyer−Schuster rearrangement, see: Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149.

(12) Substrates **2a**−**2g** were obtained from the corresponding 1,4- or 1,5-oxocarboxylic acids in 40−61% overall yields. See SI.

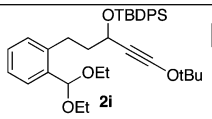
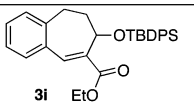
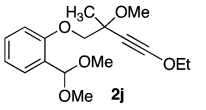
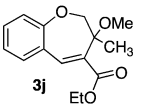
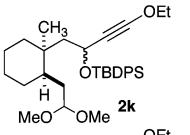
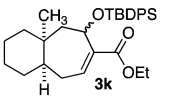
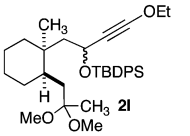
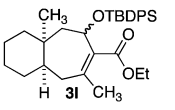
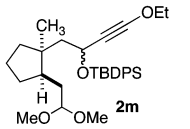
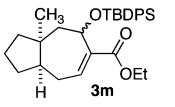
Scheme 4. Requirements for Seven-Membered Ring Formation



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 rearrangement[11] 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 alkoxycycloalkene 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 the 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 (**3m**, entry 5)

Table 3. Preparation of Seven-Membered Cycloalkenes[a]

entry	2[b]	3	yield[c]
1			72
2			61
3			68[d]
4			55[d]
5			49[e]

[a] Reaction conditions: 0.33 M **2** in CH_3CN, $Sc(OTf)_3$ (10 mol %), rt, 10 min. [b] For preparation of **2i**−**2m**, see SI and refs 13−17. [c] Isolated yield after column chromatography. [d] Compounds **2k**, **2l**, **3k**, and **3l** are composed of a 2:1 mixture of diastereomers. See text and refs 15 and 16. [e] Compounds **2m** and **3m** are composed of a 3:1 mixture of diastereomers. See text and ref 17.

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 alkoxycycloalkene 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.

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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.

The authors declare no competing financial interest

(13) Compound **2i** was prepared in 41% overall yield from 2-bromobenzaldehyde diethylacetal. See SI and (a) Mukherjee, A.; Liu, R.-S. *Org. Lett.* **2011**, *13*, 660. (b) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465.

(14) Compound **2j** was prepared in 53% overall yield from salicylaldehyde. See SI and: Martinez-Peragon, A.; Millan, A.; Campana, A. G.; Rodriguez-Marquez, I.; Resa, S.; Miguel, D.; Alvarez de Cienfuegos, L.; Cuerva, J. M. *Eur. J. Org. Chem.* **2012**, *8*, 1499.

(15) Compound **2k** was prepared in 35% overall yield from 2-allylcyclohexanone. See SI and: Asao, N.; Lee, S.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 4265.

(16) Compound **2l** was prepared in 22% overall yield from 2-allylcyclohexanone. See SI and: Smith, A. B.; Cho, Y. S.; Friestad, G. K *Tetrahedron Lett.* **1998**, *39*, 8765.

(17) Compound **2m** was prepared in 29% overall yield from 2-allylcyclopentanone. See SI.