Organic & Biomolecular Chemistry

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Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-COM-11-2022-002121.R1
Article Type:	Communication
Date Submitted by the Author:	17-Dec-2022
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COMMUNICATION

[3,3]-Sigmatropic rearrangements of propargyl alkynyl ethers. Synthesis of complex dienoates and unsaturated lactones

OBCReceived 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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In an extension of our studies on low-temperature rearrangements of 1-alkynyl ethers, we describe herein the [3,3]-sigmatropic rearrangement of *in situ* formed propargyl alkynyl ethers to allenyl ketenes, which furnish complex *tert*-butyl-(2*E*, 4*Z*)-dienoates 2 in good yields upon *tert*-butanol addition. Similarly, sigmatropic rearrangements of *in situ* formed propargyl lithioalkynyl ethers yield methyl-(2*Z*, 4*Z*)-dienoates 4 upon methanol addition or unsaturated lactones 6 upon aldehyde or ketone addition to the allenyl ynolate intermediate.

The Claisen [3,3]-sigmatropic rearrangement represents a powerful method for the formation of carbon-carbon bonds in organic synthesis.[1] Uncatalyzed Claisen rearrangements of allyl vinyl ethers to γ,δ-unsaturated aldehydes take place at temperatures typically exceeding 150 °C.[2] The sigmatropic rearrangement of allyl alkynyl ethers, in contrast, takes place rapidly at cryogenic temperatures and furnishes a ketene intermediate which may be trapped in reactions with added alcohol or amine nucleophiles to form γ,δ-unsaturated carboxylic acid derivatives.[3,4] Both processes are stereospecific and demonstrate a requirement for a cyclic transition state. DFT calculations (B3LYP/6-21G9(d) basis set) for the allyl vinyl ether rearrangement revealed an activation barrier of 29 kcal/mol, versus a 15 kcal/mol barrier for the allyl alkynyl ether rearrangement.[5a,b] Given the significantly lower temperatures required for allyl alkynyl ether sigmatropy, we recently became interested in assessing the viability of the analogous [3,3]-sigmatropic rearrangement of propargyl alkynyl ethers.[6] DFT calculations revealed an approximate activation barrier of 10 kcal/mol,[5c] indicating that this process could also be accomplished at cryogenic temperatures. In this *Communication* we provide experimental details of this novel low temperature rearrangement process, which provides complex conjugated dienes in good yields from α-propargyloxy ketones or propargyl-1,1-dichlorovinyl ether precursors.

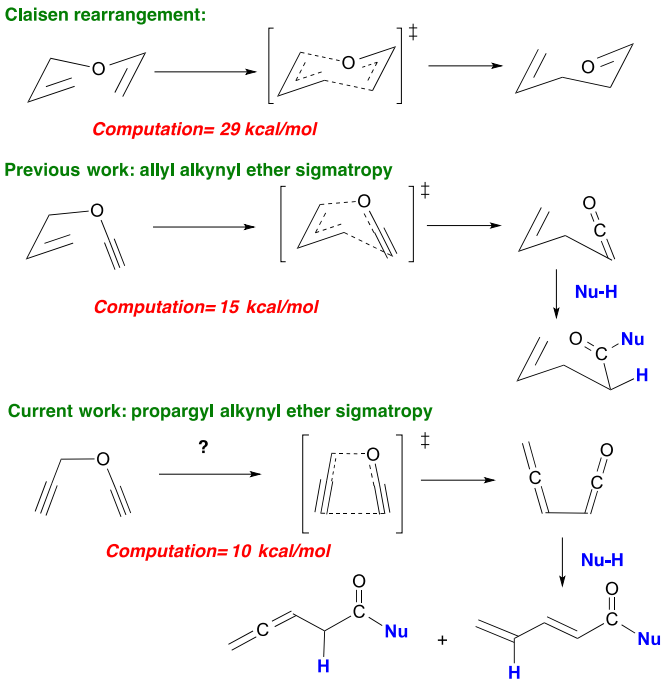

Figure 1. The Claisen rearrangement and previous work on allyl-alkynyl ether sigmatropy; current study.

In view of our previous studies on allyl-alkynyl ether sigmatropy,[4] α-propargyloxy ketones (**1**) were chosen as precursors to propargyl alkynyl ethers. These ketone substrates could be prepared in two ways: by treatment of primary and secondary proparylic alcohols with alpha-diazoketones in the presence of 10 mol% indium triflate according to the protocol of Muthusamy et. al.,[7] or by reaction of the sodium salt of

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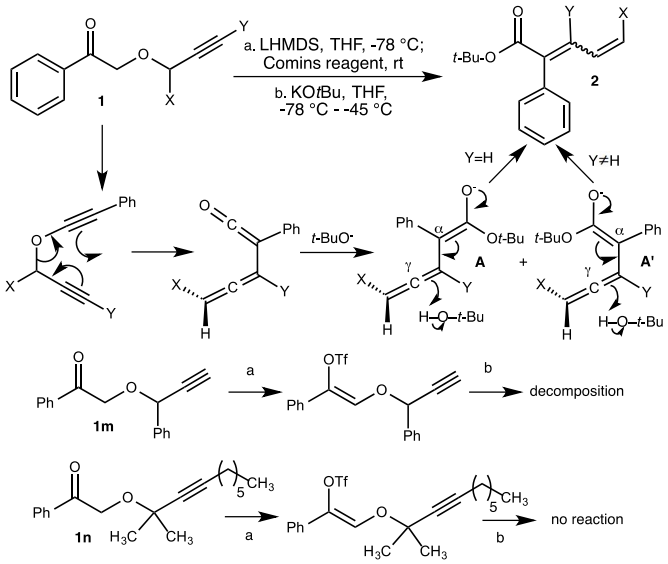
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

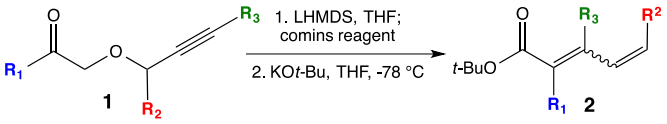
propargylic alcohols with bromoacetic acid under basic conditions, followed Weinreb amide formation and organometallic addition.[8] Thus, α-propargyloxyacetophenone (**1a**) was prepared from proparyl alcohol and diazoacetophenone in 92% yield. Treatment of **1a** with LHMDS in THF at -78°C, followed reaction with Comin's reagent[9] gave rise to the corresponding enol triflate, which after rapid filtration through a pad of silica gel and concentration *in vacuo* was treated with a 1M solution of potassium *tert*-butoxide (2.5 equivalents) in THF at -78 °C. After 30 minutes, TLC showed complete conversion to a higher rf spot; after reaction quench at -78 °C, product isolation, and purification, conjugated diene **2a** (>10:1 *E*:*Z*)[10] was obtained in 90% yield. A possible mechanistic pathway is offered in Scheme 1, in which the allenyl ketene intermediate arising from [3,3]-sigmatropic rearrangement of the propargyl alkynyl ether[25] reacts with *tert*-butoxide ion to produce allenyl ester enolate **A** that undergoes selective protonation on the γ-carbon atom of the allene (Scheme 1, X=Y=H).[11]

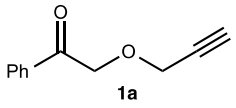
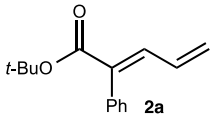
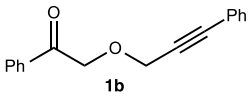
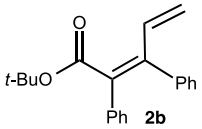
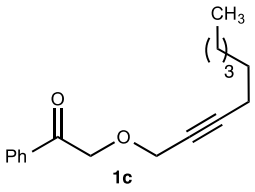
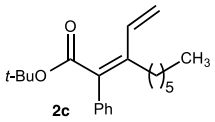
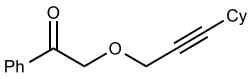
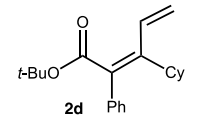
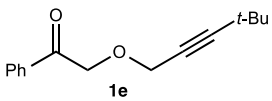
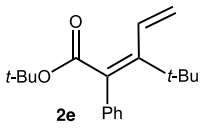
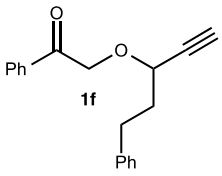
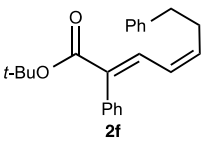
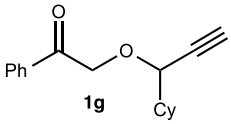
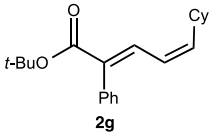
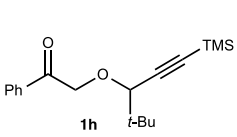
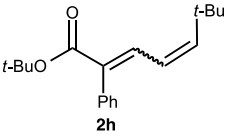


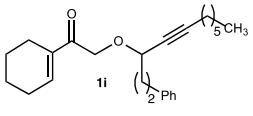
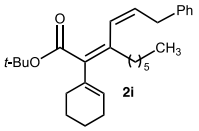
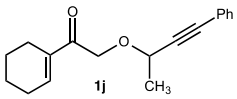
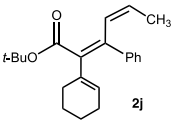
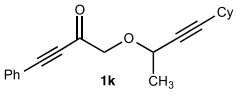
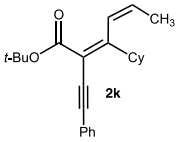
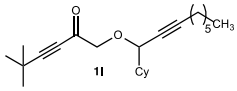
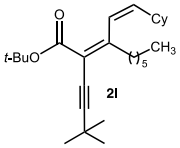
Scheme 1. Proposed mechanistic pathway for the conversion of **1** to **2**; problematic substrates **1m** and **1n**.

To explore the scope of this reaction, we prepared a series of α-propargyloxy acetophenones and subjected them to the two-step sequence of enol triflate formation and *tert*-butoxide-induced elimination (Table 1, entries 1-12). Internal alkynes with both alkyl and aryl substitution (**1b**-**1e**, entries 2-5) smoothly rearrange to dienes **2b**-**2e**, with *E* stereoisomers predominating for **2b**, **2d**, and **2e**, while the *Z* stereoisomer predominates for **2c**, indicating a preferred *syn*-orientation of the carbon group (Y) and α-phenyl in enolate **A'**.[12] Similarly, alkyne substrates bearing alkyl substitution at the propargylic position (**1f**-**1h**, entries 6-8) led to moderate to good yields of dienes **2f**-**2h**. Although the major α,β-alkene isomer possessed the *E* configuration,[12] the bulkier the propargylic substituent, the lower the *E*:*Z* selectivity (compare entries 6 and 8). Moreover, it should be noted that the γ,δ-alkene of products **2f**-**2h** (and also **2i**-**2l**) principally adopts the *Z*-configuration ($J_{\gamma,\delta}$= 11.4 - 12.0 Hz),[14] in line with the known propensity of 3,4-dienoates to isomerize to 2*E*,4*Z*-dienoates under basic conditions (likely via stereoselective protonation of enolates **A** and **A'**, Scheme 1).[11,13]

Table 1. Scope of the rearragement reactions of **1**.[a]

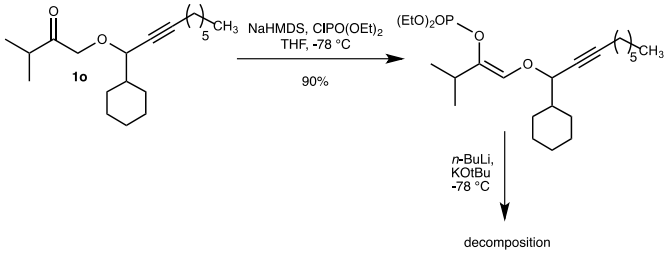


entry	1	2	Yield 2[b] (*E*:*Z*)
1			90 (>10:1)
2			69 (4:1)
3			85 (1:5)
4			72 (>10:1)
5			68 (9:1)
6			71 (5:1)
7			59 (3:1)
8			44 (1.4:1)

entry	1	2	Yield 2[a] (*E*:*Z*)
9			71 (>1:10) (1:3)[c]
10			48 (3:1)
11			55 (>1:10)
12			75 (>1:10)

[a]Ketone **1** in THF (0.3M) treated LHMDS (1.5 equiv) in THF at -78 °C for 1h, followed by addition of Comin's reagent (1.5 equiv) in 1:1 THF:HMPA (1M). After isolation and filtration through SiO_2, the enol triflate (THF, 1M) was treated with 2.5 equiv KO*t*Bu (1M,THF) at -78 °C. [b]Isolated yield after flash chromatography. [c]1:3 *E*:*Z* ratio at the γ,δ–alkene observed.

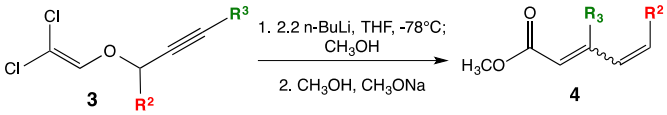
Interestingly, phenyl-substituted compound **1m** (Scheme 1) provided no rearranged diene product, likely due to preferential deprotonation of the propargylic/benzylic C-H.[3] In addition, no reaction occurred when the enol triflate corresponding to α-propargyloxy-ketone **1n** was treated with KO*t*-Bu in THF at -78 °C, indicating the steric sensitivity of deprotonation of the vinyl proton by the bulky *tert*-butoxide ion. However, this method could be extended to α-propargyloxy ketones prepared from α,β-unsaturated and acetylenic ketones as seen in entries 9-12, allowing the preparation of complex substituted dienes **2i**-**2l**.[15]

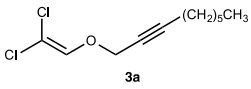
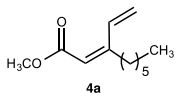
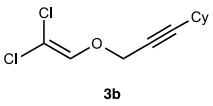
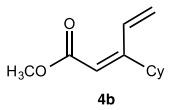
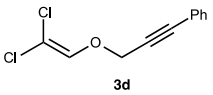
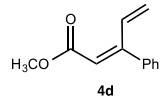
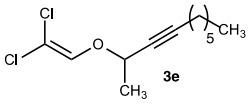
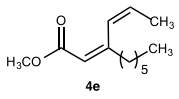
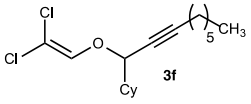
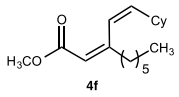
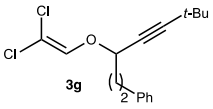
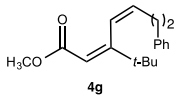
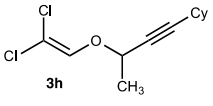
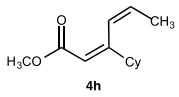
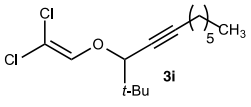
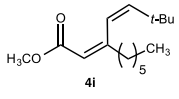


Scheme 2. Problematic substrate **1o**

Since it is known that enol triflates derived from aliphatic α-alkoxy ketones are unstable under basic conditions,[4] we next attempted to extend the scope of this protocol by the preparation of enol phosphates instead. Subjection of isopropyl ketone **1o** to NaHMDS in the presence of diethylchlorophosphate at -78 °C in THF gave a 90% yield of the corresponding enol phosphate; however, subsequent treatment with Schlosser's base (*n*-BuLi–KO*t*-Bu) gave extensive decomposition with minimal amounts of the desired diene formed. This result is likely due to preferential allylic and/or propargylic deprotonation by the highly basic reagent formed *in situ* from *n*-butyllithium and potassium *tert*-butoxide.[4]

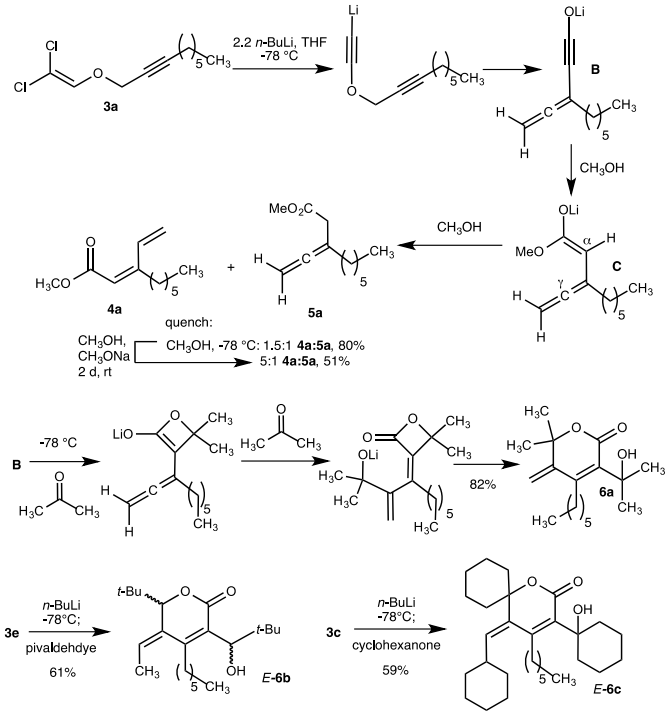
Table 2. *n*-BuLi induced rearrangements of ethers **3**.[a]



entry	3	4	yield (%) 4[b] (*E*:*Z*)
1			51 (1:5)
2			68 (5:1)
3			—
4			48 (<1:10)
5			52 (<1:10)
6			71 (>10:1) (1:2.3)[c]
7			66 (<1:10)
8			89 (<1:10)

[a] Dichlorovinyl ether **3** in THF (0.2 M) was treated with *n*-BuLi (2.2 equiv) at -78 °C. After 10 minutes methanol was added and the mixture warmed to rt. After isolation the crude material was dissolved in methanol and a catalytic amount of sodium hydride was added. The mixture was stirred for 48 h. [b] Isolated yield after flash chromatography. [c]1:2.3 *E*:*Z* ratio at the γ,δ alkene observed.

It was subsequently found that propargyl-1,1-dichlorovinyl ethers, prepared in high yields from the corresponding propargyl formate esters,[16] also serve as excellent precursor substrates for the sigmatropic rearrangement reaction.[3,17] Treatment of **3a** (Scheme 3) with 2.2 equiv. *n*-BuLi at -78 °C for 10 minutes, followed by reaction quench with methanol and warming to room temperature, gave rise to a 1.5:1 mixture of dienoate **4a** and allene **5a** in 80 % yield; stirring the crude mixture in methanol with a catalytic amount of sodium methoxide at room temperature for 48 hours gave a 5:1 ratio of **4a** and **5a** in 51% yield. The predominant formation of the *Z*-**4a** stereoisomer may be rationalized based on preferred γ-protonation of ester enolate **C**, in which the alkyl group and enolate α-hydrogen atom are *syn*.



Scheme 3. Sigmatropic rearrangements of propargyl-1,1-dichlorovinyl ethers and carbonyl trapping reactions.

Table 2 shows the scope of the *n*-butyllithium induced rearrangement of propargyl-1,1-dichlorovinyl ethers in terms of the yields of dienoates produced after treatment of the crude products with methanol and catalytic sodium methoxide at room temperature for 48 hours. A variety of dichlorovinyl ethers participate in the rearrangement process, giving rise to dienoates **4a – 4b** and **4e**-**4i**, with *Z*-stereoisomers predominating at the α,β-alkene (with the exception of **4b** and **4g**) and with the *Z*-configuration predominantly observed at the γ,δ-alkene of **4e** through **4i**.[18] Notably, treatment of phenyl substituted substrate **4d** with *n*-BuLi followed by addition of methanol led to decomposition, most likely due to proton transfer from the propargylic position to the initially formed dichlorovinyl ether anion; similar results were obtained previously on attempted rearrangements of cinnamyl dichlorovinyl ethers.[3]

Finally, we have recently shown that allylic ynolates,[19-21] generated by base-induced [3,3]-sigmatropic rearrangement of allyl-1,1-dichlorovinyl ethers, undergo [2+2] cycloaddition reactions with carbonyl compounds to furnish unsaturated carboxylic acids.[22] Similarly, quenching the rearrangement reactions of **3** with ketones or sterically encumbered aldehydes[23] instead of methanol gave rise to complex unsaturated lactones **6** via a carbonyl-ynolate [2+2] cycloaddition followed by reaction of the resulting allenolate with a second equivalent of the aldehyde or ketone and translactonization. Lactone **6a** (arising from dichlorovinyl ether **3a** and acetone), lactone *E*-**6b** (as a 1:1 mixture of diastereomers, arising from dichlorovinyl ether **3e** and pivaldehyde) and lactone *E*-**6c** (arising from dichlorovinyl ether **3c** and cyclohexanone) were prepared in this fashion in 82, 61, and 59% yields, respectively.[24] Attempts to expand the scope of this process by employing two different carbonyl substrates via sequential addition to the reaction led to complex mixtures and low yields.

Conclusions

Propargyl alkynyl ethers generated *in situ* by base treatment of propargyl enol triflates undergo [3,3]-sigmatropic rearrangements to allenyl ketenes, which produce principally 2*E*,4*Z*-dienoates in good yields after ketene trapping and protonation. Similarly, propargyl dichlorovinyl ethers undergo *n*-BuLi induced [3,3]-sigmatropic rearrangements to furnish principally 2*Z*,4*Z*-dienoates after basic methanol treatment or unsaturated δ-lactones after treatment with ketones and sterically hindered aldehydes. These processes further highlight the utility of ynol ether and ynolate intermediates in low-temperature carbon-carbon bond-forming processes.

Acknowledgements

We gratefully acknowledge the National Science Foundation (CHE-2003261) and the ACS-PRF (62233-UR1) for their generous support of this research. We also acknowledge both the UC Riverside and Caltech Mass spectrometry facilities for providing accurate mass data.

Conflicts of interest

There are no conflicts to declare.

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24 NOESY spectra (see Electronic Supplementary Information) confirmed the *E*-configuration of the exocyclic olefin of compounds **6b** and **6c**.
25 Given the structural similarity of the *in-situ* formed propargyl alkynyl ethers and enediynes which undergo the Bergman cycloaromatization, we tested for the possibility of diradical intermediates in this process by the addition of 1 equivalent of TEMPO to the elimination reaction (KO*t*-Bu, THF, -78 °C – 0 °C) of the enol triflate of ketone **1a**. Product **2a** was formed in 90% yield, and no products arising from TEMPO trap were detected by ^{1}H NMR. We gratefully acknowledge a reviewer for pointing out this mechanistic possibility.