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Low-Temperature *n*-Butyllithium-Induced Rearrangement of Allyl 1,1-Dichlorovinyl Ethers

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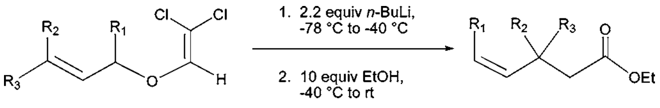
ABSTRACT



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Upon treatment with *n*-BuLi at low temperatures, a variety of allyl 1,1-dichlorovinyl ethers 2 undergo rearrangement to furnish γ,δ-unsaturated esters 3 after alcohol addition. Compounds containing quaternary centers (3e: R_1 = H, R_2, R_3 = –$(CH_2)_5$–; 3f: R_1 = H, R_2 = CH_3, R_3 = $(CH_2)_2CH(CH_3)_2$) may be formed in high yield and under mild conditions utilizing this protocol. The reaction is stereospecific and may be applied to the preparation of $\Delta^{2,3}$-*β*-*C*-glycosides and α,*β*-disubstituted lactones.

The [3,3] sigmatropic rearrangement of allyl vinyl ethers (the Claisen rearrangement) is a powerful strategy for forming carbon−carbon bonds that has been extensively used in the synthesis of complex molecules (Figure 1, eq 1).[1] Uncatalyzed Claisen rearrangements typically require heating of allyl vinyl ether substrates in excess of 100 °C. Variants of the allyl vinyl ether rearrangement can be performed at significantly lower temperatures under conditions that allow excellent stereocontrol and that are compatible with complex substrates containing thermally sensitive functionality.[2] Despite the enormous practical utility of these processes, the [3,3]-sigmatropic rearrangement of the analogous allyl alkynyl ethers has not been explored extensively (Figure 1, eq 2).

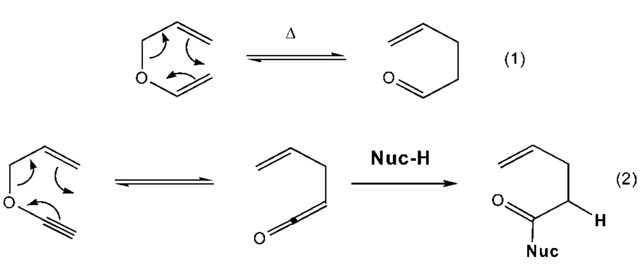

Figure 1. [3,3]-Sigmatropic rearrangements.

Early investigations by Arens[3] and Schmid[4] revealed that substituted and unsubstituted benzyl alkynyl ethers undergo sigmatropic rearrangement followed by intramolecular ketene trapping to form indanones in high yield. Although Arens refers to the rapid low-temperature rearrangements of allyl alkynyl thioethers,[5] to our knowledge, there have been no formal reports of aliphatic [3,3]-sigmatropic rearrangements of allyl alkynyl ethers. In this paper, we describe our attempts to study this potentially useful process.

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(1) For reviews of the Claisen Rearrangment, see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43. (c) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461. (d) Nubbemeyer, U. *Synthesis* **2003**, 961.

(2) (a) Wipf, P. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 827. (b) Wilson, S. R. *Organic Reactions*; John Wiley & Sons: New York, 1993; Vol. 43, p 93. (c) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971.

(3) Olsman, H.; Graveland, A.; Arens, J. F. *Rec. Trav. Chim. Pays-Bas* **1964**, *83*, 301.

(4) Wunderli, A.; Zsindely, J.; Hansen, H. J.; Schmid, H. *Chimia* **1972**, *26*, 643.

(5) Brandesma, L.; Bos, H. J.; Arens, J. F. In *The Chemistry of Acetylenes;* Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 751−860.

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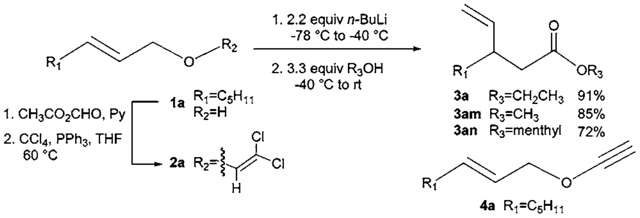
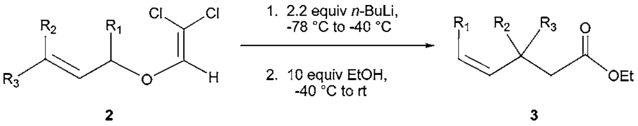
A current practical method for the preparation of terminal and internal alkynyl ethers involves treatment of dichlorovinyl ethers with excess *n*-BuLi followed by quenching with an alcohol or an electrophile.[6,7] We thus decided to synthesize allyl dichlorovinyl ethers as direct precursors of allyl alkynyl ethers. Greene's method for forming 1,2-dichlorovinyl ethers, involving reaction of potassium alkoxides with trichloroethylene,[8] proved unsatisfactory when applied to allylic alcohols.[9] Instead, Bruckner's mild two-step protocol involving alcohol formylation (acetic formic anhydride[10]/pyridine) and subsequent dichlorovinylation (PPh_3/CCl_4) furnished high yields of allyl 1,1-dichlorovinyl ethers **2**[11] from a variety of allylic alcohols **1** (Scheme 1).[12] Addition of 2.2 equiv of *n*-BuLi to a THF solution of allyl 1,1-dichlorovinyl ether **2a** at −78 °C, followed by warming to −40 °C and quenching with excess ethanol, gave, after aqueous workup, not the expected terminal alkynyl ether **4a** but rather rearranged ester **3a** in 91% yield.[13] Quenching the reaction mixture with methanol or menthol instead of ethanol gave rise to the corresponding rearranged esters **3am** and **3an** in 85% and 72% yields, respectively.

Scheme 1. Rearrangement of Substrate **2a**



Subjection of a variety of cyclic and acylic allyl dichlorovinyl ethers to these reaction conditions gave similarly high yields of rearrangement products (Table 1); notably, compounds containing quaternary centers (Table 1, entries 5 and 6) can be formed efficiently using this protocol. Interestingly, exposure of the corresponding dibromovinyl ethers to the same reaction conditions gave <10% of the rearranged homoallylic esters, providing instead a cis/trans mixture of monodebromination products.[14] Dichlorovinyl ether **2g** derived from cinnamyl alcohol (Table 1, entry 7) also failed to furnish useful amounts of rearranged product, likely because of intramolecular allylic deprotonation by the initially formed vinyl anion.[15]

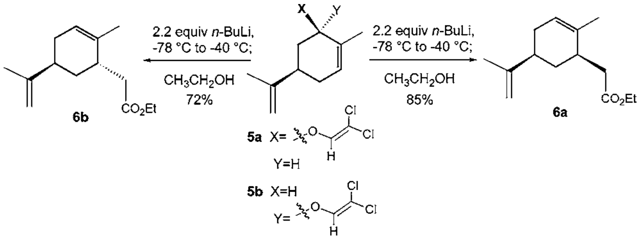
Table 1. Scope of the Rearrangement of Allyl 1,1-Dichlorovinyl Ethers



entry	2	3	R_1	R_2	R_3	yield (%)
1	**2a**	**3a**	H	H	C_5H_{11}	91
2	**2b**	**3b**	H	H	*t*-$BuSiPh_2OCH_2$	90
3	**2c**	**3c**	H	*t*-$BuSiPh_2OCH_2$	H	95
4	**2d**	**3d**	$-(CH_2)_3-$		H	92
5	**2e**	**3e**	H	$-(CH_2)_5-$		85
6	**2f**	**3f**	H	CH_3	$(CH_3)_2CH(CH_2)_2$	75
7	**2g**	**3g**	H	H	Ph	

In light of these results, we explored the stereospecificity of this process by independently subjecting diastereomerically pure dichlorovinyl ethers to the rearrangement protocol. Upon treatment with *n*-BuLi followed by ethanol quench, *cis*-carvyl dichlorovinyl ether **5a** produced rearranged *cis*-ethyl ester **6a** exclusively, while *trans*-carvyl dichlorovinyl ether **5b** furnished rearranged *trans*-ethyl ester **6b** exclusively (Scheme 2).[16] These results indicate that the rearrangement is indeed highly stereospecific, with carbon−carbon bond

Scheme 2. Stereospecific Rearrangements



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(6) For a review of methods for the synthesis of ynol ethers, see: Stang, P. J.; Zhdankin, V. V. *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons: New York, New York, 1994; Chapter 19.

(7) (a) Smithers, R. H. *Synthesis* **1985**, 556. (b) Himbert, G.; Loffler, A. *Synthesis* **1992**, 495.

(8) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2, 2919.

(9) Only trace amounts of 1,2-dichlorovinyl ethers were formed using the Greene protocol, with starting allylic alcohols recovered in >90% yield from the reaction mixture.

(10) Huffman, C. W. *J. Org. Chem.* **1958**, *23*, 727.

(11) The allyl 1,1-dichlorovinyl ethers prepared were stable at room temperature and at 60 °C in THF under the conditions for their formation from the corresponding formate esters. The [3,3]-sigmatropic rearrangement of allyl 1,1-dichlorovinyl ethers at temperatures >100 °C has been described: Morimoto, T.; Sekiya, M. *Synthesis* **1981**, 308.

(12) Bruckner, D. *Synlett* **2000**, 1402. See also: Lakhrissi, M.; Chapleur, Y. *J. Org. Chem.* **1994**, *59*, 5752.

(13) (a) The use of LDA instead of *n*-BuLi under the same reaction conditions failed to afford rearrangement products. (b) It was subsequently found that warming the reaction to −40 °C before quench with ethanol was unnecessary; high yields of rearranged products **3** are consistently obtained after stirring the reaction mixture for 15−30 min at −78 °C followed by ethanol quench and warming to room temperature (vide infra).

(14) A similar result was noted by Bruckner in an attempted synthesis of alkynylsulfonamides from dibromovinyl sulfonamides; see ref 12.

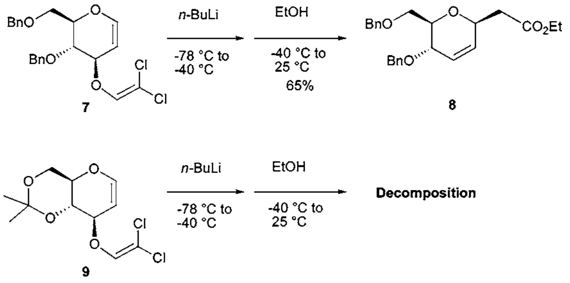
(15) Treatment of **2g** with *n*-BuLi at −78 °C gave a dark-colored solution (presumably due to formation of a highly delocalized carbanion), which upon ethanol quench furnished a cis/trans mixture of monodechlorination products.

(16) (a) **5a** and **5b** were obtained from *cis*- and *trans*-carveol, respectively, by treatment with acetic formic anhydride/pyridine followed by PPh_3/CCl_4/THF (see supporting info for details). *cis*-Carveol was synthesized by stereoselective reduction of (*R*)-(−)-carvone: Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. *trans*-Carveol was prepared by Mitsunobu inversion/hydrolysis of *cis*-carveol: Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633. (b) ^1H NMR data for **6a** and **6b** matched those reported by Bermejo: Rico, R.; Zapico, J.; Bermejo, F.; Sanni, S. B.; Garcia-Granda, S. *Tetrahedron: Asymmetry* **1998**, *9*, 293.

formation occurring on the same face of the molecule as carbon−oxygen bond cleavage.

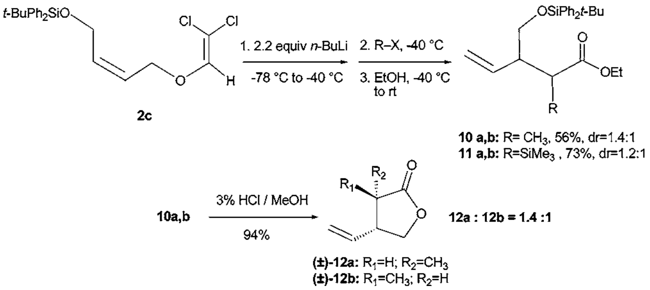
To explore the potential application of this process to the synthesis of C-glycosides, we subjected glucal derivatives **7** and **9** to the rearrangement protocol (Scheme 3). Exposure of 3,4-dibenzyl glucal **7** to *n*-BuLi at −78 °C followed by ethanol quench at −40 °C gave rise to $\Delta^{2,3}$-*C*-glycoside **8** with exclusive β-anomeric stereochemistry in 76% yield.[17] In contrast, conformationally restricted glucal **9** gave none of the desired rearrangement product when subjected to the same conditions; TLC analysis indicated that a compound other than **9**[18] present at −40 °C after ethanol quench was decomposing as the reaction mixture was warmed to ambient temperatures. Clearly, geometric factors in the substrate are important for the rearrangement, and this result points toward the existence of a pathway involving a cyclic transition state. For glucal derivatives, such a transition-state geometry may only be achieved by ring flip, which is impossible for substrate **9**.

Scheme 3. *C*-Glycoside Synthesis



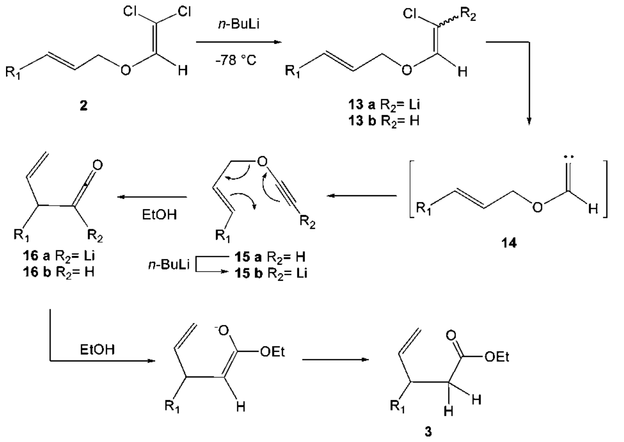
Finally, to assess if the anionic intermediate generated upon *n*-BuLi treatment of allyl dichlorovinyl ethers would react with electrophiles other than the proton, the rearrangement reaction of **2c** was performed with addition of either methyl triflate (2.0 equiv) or TMSCl (2.0 equiv) at −40 °C prior to addition of ethanol (Scheme 4). Indeed, α-substituted ethyl esters **10a**,**b** and **11a**,**b** were isolated in 58% and 73% yields, respectively; in each case a ∼1:1 mixture of diastereomers was obtained.[19] Exposure of **10a**,**b** to 3% HCl in CH_3OH for 7 h at room temperature gave a separable 1.4:1 cis/trans mixture of racemic butyrolactones **12a** and **12b**.[20]

Scheme 4. Rearrangement with Electrophile Incorporation



Although the mechanism of this rearrangement has not been established,[21] the low temperature at which the reaction occurs suggests that a pathway different from that originally proposed by Arens and Schmid for benzyl alkynyl ether sigmatropy (Scheme 5, **15** → **16b**)[22] may be operative. In experiments to probe the reaction mechanism, it was found that treatment of dichlorovinyl ether **2a** with 3 equiv of *n*-BuLi in THF at −78 °C for 10 min followed by addition of excess ethanol gave, upon warming to room temperature, a 10:1 mixture of rearranged product **3a** and monochlorovinyl ether **13b** (Scheme 5, $R_1{=}C_5H_{11}$). Treatment of **2a** instead with 1.5 equiv *n*-BuLi in THF at −78 °C for 10 min followed by ethanol quench and warming to room temperature gave a ∼1:1 mixture of **2a**/**3a**; again, approximately 9% of the reaction mixture consisted of monochlorovinyl ether **13b**. These results, and also the observation that the use of LDA instead of *n*-BuLi in the reaction does not furnish rearrangement products,[12] suggest that halogen−metal exchange is a likely first step in the mechanism. Once formed, the alkenyllithium species **13a** may undergo transformation to another intermediate that consumes an additional 1 equiv of *n*-BuLi before the next transmetalation can take place. A possible reaction pathway, outlined in Scheme 5, involves

Scheme 5. Possible Mechanism for the *n*-BuLi-Induced Rearrangement of Allyl 1,1-Dichlorovinyl Ethers



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[17] In a two-dimensional NMR (NOESY) experiment performed on **8**, an NOE was observed between carbohydrate H_1' and H_5', thus confirming the assignment of the β stereochemistry shown above. See the Supporting Information for details. For a discussion of the stereochemical assignment of 2,3-unsaturated C-glycosides, see: Brakta, M.; Farr, R. N.; Chaguir, B.; Massiot, G.; Lavaud, C.; Anderson, W. R.; Sinou, D.; Daves, G. D. *J. Org. Chem.* **1993**, *58*, 2992.

[18] Based on our proposed mechanism (Scheme 5, vide infra), we suggest that this unstable species present at low temperature is an allyl alkynyl ether (e.g., **15a**, Scheme 5).

[19] Trapping the anionic intermediate with benzaldehyde (1.5 equiv, 1 h, −78 °C, followed by 1.5 equiv of TMSCl, −78 to +25 °C) was also successful, giving rise to a mixture of aldol diastereomers.

[20] The stereochemistry of **12a** and **12b** was assigned by comparison of their ^1H NMR spectral data with literature values: Tamaru, Y.; Furukawa, Y.; Mizutani, M.; Kitao, O.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 3631.

[21] Attempts to trap the anionic intermediate by reaction with acetyl chloride, tosyl chloride, ethyl chloroformate, TIPS-Cl, or TBDPS-Cl led only to a complex mixture of unidentifiable products.

[22] See refs 3 and 4 above.

formation of an allyl alkynyl ether **15a** (via carbene **14**), followed by deprotonation (→ **15b**) and accelerated rearrangement,[23] producing lithioketene **16a** prior to addition to ethanol; protonation (**16** → **16b**), ethoxide trap of the ketene, and ester enolate protonation would furnish the product. Experiments to elucidate the latter part of the pathway shown, in particular to distinguish whether species **15a** or **15b** is undergoing sigmatropic rearrangement, are currently underway.

This rearrangement reaction occurs at low temperatures and under mild conditions, affording high yields of products containing up to two new carbon−carbon bonds. A potential advantage of this method over other variants of the Claisen rearrangement[2] is the ability to add a variety of alcohol nucleophiles to the proposed ketene intermediate, allowing the one-pot preparation of diverse esters of γ,δ-unsaturated carboxylic acids (Scheme 1, **3a**, **3am**, and **3an**). Further studies on the utility and the scope of this reaction are in progress.

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Supporting Information Available: Experimental details for all reactions as well as characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] As of yet we can suggest no obvious kinetic advantage for the rearrangement to occur via the lithioalkynyl ether. A number of anion-accelerated [3,3]-sigmatropic rearrangements are known and take place at temperatures below their neutral counterparts: (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609. (c) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.1. (d) Wilson, S. R. *Org. React.* **1993**, *43*, 93.