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SYNTHESIS AND CLAISEN REARRANGEMENT OF 1-ALLYLOXY-1-CARBOMETHOXY ALLENES

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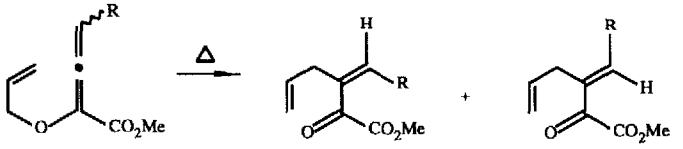
Abstract: A number of allyl allenyl ethers (1) have been synthesised and shown to undergo the Claisen rearrangement. The kinetics of rearrangement of (1b) together with stereochemical data obtained, is consistent with a concerted mechanism for these rearrangements.

A number of variants of the Claisen rearrangement in which the olefinic π systems of allyl vinyl ether are replaced by other π systems are known. For example, the allyl group has been replaced by propargyl[1], benzyl[2] and allenyl[3] groups, while the vinyl has been replaced by aryl[4] and ethynyl[2] groups. It is clear from these rearrangements that the geometric constraints on the 6-membered Claisen transition state are not severe. This being so, another possible substrate variation would be replacement of the vinyl group by an allenyl group. Thus, allyl allenyl ethers (1) might be expected to undergo Claisen rearrangement (Scheme 1). Such a rearrangement has not been reported and prior to this work, compounds such as (1) had not been synthesised.



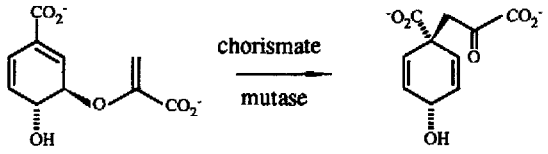
(1) Z-(2) E-(2)

(a) R=Ph, (b) R=^{t}Bu, (c) R=Me, (e) R=H.

Scheme 1

From a chemical standpoint, demonstration of the rearrangement (1) → (2) would further delineate the geometric constraints on the transition state for the Claisen rearrangement. In addition, it could lead to the development of useful synthetic methodology. Thus the rearrangement product (2) contains an activated α,β-unsaturated carbonyl group which would be capable of further synthetic elaboration, eg. by Michael addition of appropriate nucleophiles.

This same Michael reactivity of (2) has the potential to make compounds such as (1) suicide substrates[5] for the chorismate mutase enzymes[6]. These key enzymes of the Shikimate Pathway[7] which is obligate[7] for the biosynthesis of aromatic amino acids in higher plants and microorganisms, catalyse the rearrangement of chorismate to prephenate (Scheme 2) - formally a Claisen rearrangement. The detailed mechanism of this rearrangement has been the subject of intense recent study[8].

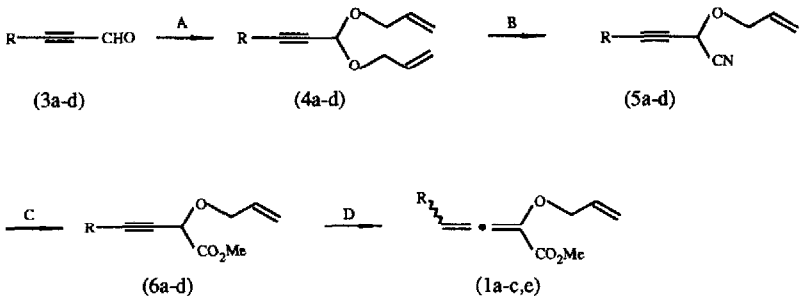


chorismate prephenate

Scheme 2

If an allenic analogue of chorismate (such as (1)) could act as a substrate for these enzymes, rearrangement product (2) would be generated at the respective enzyme active sites. Reaction of this Michael acceptor with nucleophilic groups (amino acid side chains) at the active site could result in irreversible trapping of (2) at the active site, thus destroying the catalytic activity of the enzyme. Suitably elaborated analogues of (1) are presently being synthesised to examine this possibility.

We report here a general synthesis (Scheme 3), and Claisen rearrangement (Scheme 1), of 1-allyloxy-1-carbomethoxy allenes (1).



(3a-d) (4a-d) (5a-d)

(6a-d) (1a-c,e)

A. Allyl alcohol, *p*TsOH, benzene, reflux.
B. TMSCN, BF_3:OEt_2.
C. HCl/MeOH, reflux.
D. 1. ^{t}BuLi or LDA, THF, -78°C. 2. MeOH, -78°C.

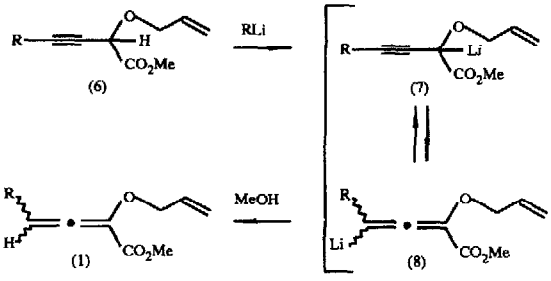
(a) R=Ph
(b) R=^{t}Bu
(c) R=Me
(d) R=TMS → (e) R=H

Scheme3

Propargyl aldehydes (3) were transformed to their corresponding diallyl acetals (4)[9] using conventional methodology. Subsequently, one allyloxy group of (4) could be exchanged for nitrile by boron trifluoride-catalysed reaction with trimethylsilylcyanide (TMSCN). This reaction had previously been reported for dimethyl and diethyl acetals[10]. Hydrolysis of (5) with HCl in refluxing methanol gave allyl 1-carbomethoxy propargyl ethers (6) which were metallated with 1 equivalent of ^{t}BuLi or LDA in THF at -78°C. The resulting carbanion mixture (Scheme 4) was quenched with methanol, also at -78°C, resulting in exclusive allene formation[11] (Scheme 4). Similar metallations of propargyl ethers lacking the carbomethoxy functionality results in a mixture of allenic and propargylic products after condensation with aldehydes[12] or quenching with methanol-ice[13]; previously, exclusive allenic products have been reported from quenching with hard electrophiles such as TMSCl[14a,b]. The latter observation has been rationalized by attributing greater hard character to allenic (sp^2) compared to propargylic (sp^3) carbanions.

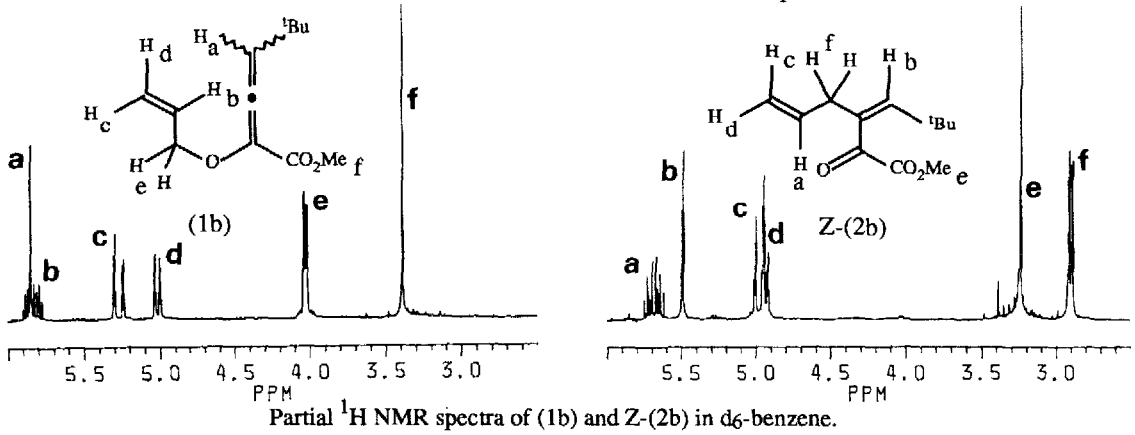
Attempted isomerization of the trimethylsilyl analogue (6d), by the same approach, resulted in loss of the TMS group, yielding the parent allene (1e). Presumably, (1e) results from nucleophilic attack at silicon followed by proteotropic rearrangement (perhaps during workup). This suggestion is supported by the fact that reaction of (6d) with $(Bu)_4NF$[15] also yields (1e) as the only product. Such a reaction is not altogether surprising since the intermediate acetylenic anion

constitutes a good leaving group. However this result is in contrast to a previous communication[14a] in which silylated propargyl ethers were metallated by nBuLi at the propargyl carbon, leaving the silyl group intact.



Scheme 4

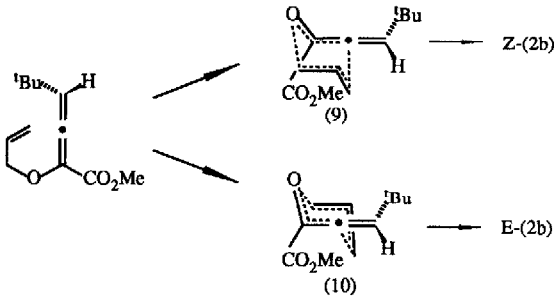
Allene (1a) was found to be extremely unstable and decomposed within hours of preparation and purification. This instability could be due to the presence in (1a) of multiple conjugated functionality which may confer on it thermal (and perhaps photochemical) reactivity. Allenes (1b,c and e), all of higher stability[16], undergo the proposed Claisen rearrangement in d_6-benzene (containing 0.03% t-butyl catechol) at temperatures as low as 70°C. Rearrangement of (1b)[17] yields, in an exceptionally clean reaction, only the Z-isomer of (2b)[18]. The reaction can be followed by ^1H NMR spectroscopy (300MHz, d_6-benzene). Diagnostic spectral changes include the disappearance of allenic H signal (a) at δ5.85 (s) and the allylic CH_2 signal (e) at δ4.02 (d."q".; 5.2, 1.6Hz) of (1b) and the appearance of the vinylic H signal (b) at δ5.50 (t; 1.3Hz) and the doubly allylic CH_2 signal (f) at δ2.90 (d."q".; 6.7, 1.3Hz) of Z-(2b) (see Figure 1). The kinetics of this rearrangement have been studied in some detail, and the activation parameters (E_a=95±5kJmol^{-1}, $\Delta S^{\ddagger}$=-60±6JK^{-1}mol^{-1}) for the first order reaction are indicative[19] of a concerted process.



Partial ^1H NMR spectra of (1b) and Z-(2b) in d_6-benzene.

Figure 1

Examination of molecular models reveals that the chair-like transition state (10) leading to the E isomer of (2b) (see Scheme 5) suffers destabilizing steric interactions from the bulky t-butyl group. These interactions are absent from the diastereomeric transition state (9) which would afford the Z isomer. Rearrangement of (1c) yields both the Z and E isomers of (2c) in the approximate ratio of 4:1[20]. This product ratio is consistent with the transition state model discussed for rearrangement of (1b), given the smaller bulk of the methyl substituent relative to t-butyl. Rearrangement of the parent allene (1e), occurs under comparable conditions, but like that of (1c), is accompanied by significant formation of by-products.



Scheme 5

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9. Satisfactory ^{1}H and ^{13}C NMR data were obtained for all new compounds. High resolution mass spectra were also obtained where thermal stabilities of the compounds allowed.

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11. Diagnostic NMR signals (300MHz, $CDCl_3$) include the signal for the propargyl H in (6b) (δ4.73, singlet) and that of the allenyl H in (1b) (δ6.13, singlet). The ^{13}C NMR of (1b) (75MHz, $CDCl_3$) contains a quaternary carbon signal at 193.4ppm, corresponding to the central carbon of the allene system.

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14. a) Mantione, R. and Leroux, Y., *Tetrahedron Lett.*, 1971, 593. b) Leroux, Y. and Roman, C., *Ibid.*, 1973, 2585.

15. Hanessian, S. and Lavallee, P., *Can. J. Chem.*, 1975, *53*, 2975.

16. Although (1b,c and e) were more stable than (1a), certain precautions were still necessary to prevent polymerization and/or decomposition: The compounds were stored at -5°C under a nitrogen atmosphere as dilute hexane solutions containing t-butylcatechol (0.03%).

17. This rearrangement was first reported at the RACI Division of Organic Chemistry 10th National Conference, University of New South Wales, August 1987, abstract TP42.

18. NOE experiments (300MHz, $CDCl_3$) confirming structure of (2b): Irradiation at δ2.97 (H_f; see figure 1) affords a NOE enhancement at δ5.63 (H_b; 5.4%). Irradiation at δ5.63 (H_b) affords a NOE enhancement at δ2.97 (H_f;3.1%).

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20. NOE experiments (300MHz, $CDCl_3$): Major isomer; irradiation at δ3.06 (doubly allylic CH_2) affords a NOE enhancement at δ6.35 (vinyl H geminal to CH_3; 3.2%). Irradiation at δ6.35 (vinyl H geminal to CH_3) affords a NOE enhancement at δ3.06 (doubly allylic CH_2; 1.0%). Minor isomer; irradiation at δ3.12 (doubly allylic CH_2) affords a NOE enhancement at δ1.97 (allylic CH_3; 1.6%). Irradiation at δ1.97 (allylic CH_3) affords a NOE enhancement at δ3.12 (doubly allylic CH_2; 2.9%).

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