Observations on the Synthesis and Carbocyclisation Reactions of 6-Oxohexa-2,3-dienoates

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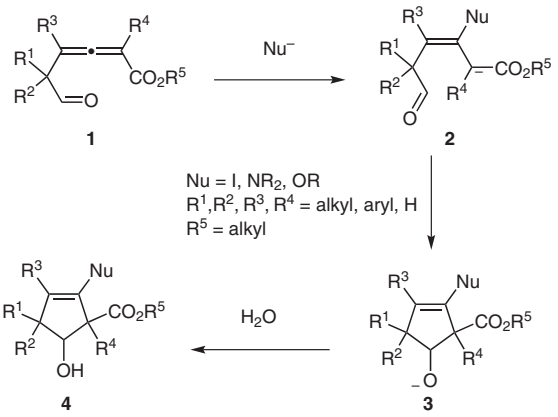
Dedicated to Professor Sir Jack Baldwin FRS on the occasion of his 70th birthday

Abstract: 6-Oxohexa-2,3-dienoates can be readily prepared via an atom economical Claisen rearrangement of propargyl vinyl ethers formed in situ by the reaction of propargylic alcohols with acetals. Preliminary experiments have demonstrated that these functionalised allenic esters undergo a facile amine-induced carbocyclisation under mild reaction conditions, yielding densely functionalised cyclopentanones containing chiral quaternary carbon centres.

Key words: acetals, alcohols, allenes, cyclisation, rearrangements

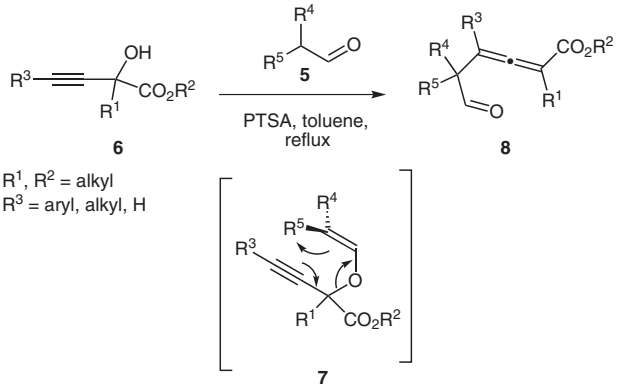
The presence of two π electron clouds separated by a single sp hybridised carbon atom is the identifying structural characteristic of allenes, and it is this unique structural and electronic arrangement that is responsible for the extraordinary reactivity profile displayed by allenic compounds.[1] The synthetic potential of electron-deficient allenes has been explored extensively in recent years, and this has led to the development of novel methods for the construction of a variety of functionalised heterocyclic and carbocyclic systems.[2] As part of our ongoing research programme on the application of allenes to the construction of complex ring systems,[3] we envisaged that functionalised allenic esters **1** would provide opportunities for the development of novel cyclisation strategies (Scheme 1). It was anticipated that allenic esters **1** would undergo cyclisation reactions to give cyclopentenols **4**, via tandem sequences involving the addition of nucleophiles to the central allenic carbon, followed by cyclisation of the resulting ester enolates **2** onto the pendant carbonyl. Furthermore, it was expected that the electronic properties of the resulting double bond in the cyclopentenol **4**, would depend on the identity of the added nucleophile and the substituents on the allene, and in consequence, a range of carbocyclic systems could be obtained by changing these variables.

A plethora of methods exists for the construction of allenic esters, including the base-mediated isomerisation of acetylenic acids and esters, transition-metal-mediated carbonylation reactions of propargylic derivatives and the Wittig or Horner–Wadsworth–Emmons olefination of ketenes.[4]



Scheme 1

We have previously shown that the synthetically versatile 6-oxo-2-hexenoate moiety can be readily accessed via Claisen rearrangement of allyl vinyl ethers, formed in situ through the reaction of substituted allylic alcohols and α-disubstituted aldehydes.[5] It was envisaged that the analogous allenic esters **8** would be obtained by reacting propargylic alcohols **6** and aldehydes **5**, via intermediate propargyl vinyl ethers **7** (Scheme 2). It was anticipated that this protocol would enable a rapid efficient assembly of a variety of structurally diverse allenic esters **8**, allowing for a detailed study of their potential to act as precursors to substituted cyclopentenols **4**. Precedent exists for such an approach to the synthesis of allenic compounds,[6] however, to the best of our knowledge, the use of propar-



Scheme 2

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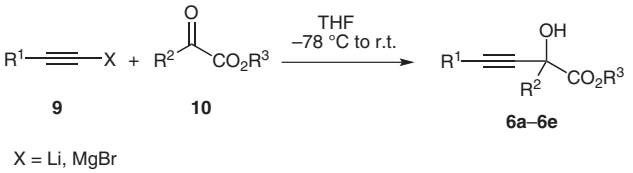
gylic alcohols bearing an electron-withdrawing group such as **6**, to give the corresponding acceptor-substituted allenes **8** has not been reported.

In order to assess this approach towards the target allenic esters **8**, a range of propargylic alcohols **6a–e** was prepared by the reaction of metallated acetylenes **9** with commercially available pyruvic acid esters **10** (Scheme 3 and Table 1).[7]



9 10 6a–6e

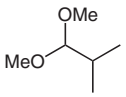
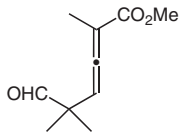
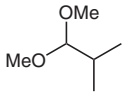
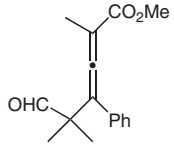
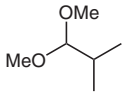
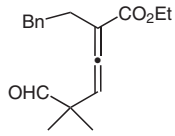
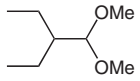
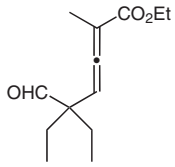
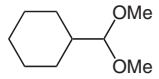
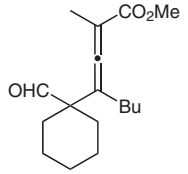
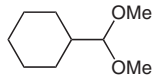
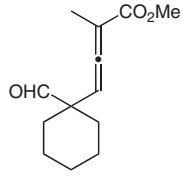
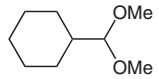
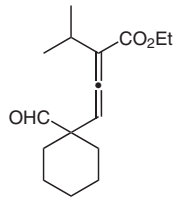
Scheme 3

Table 1 Preparation of Propargylic Alcohols **6a–e** from Metallated Acetylenes **9** and Pyruvic Acid Esters **10**

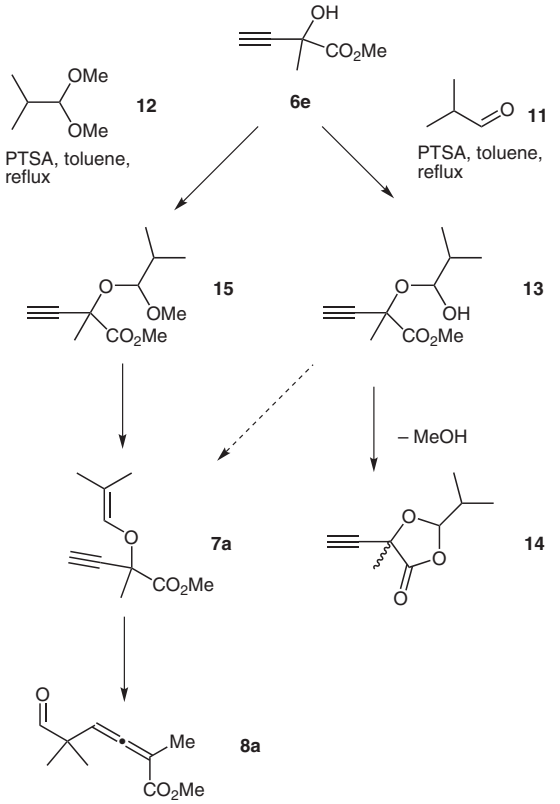
Product	R^1	R^2	R^3	Yield (%)
6a	Ph	Me	Me	88
6b	*n*-Bu	Me	Me	40
6c	H	CH_2Bn	Et	62
6d	H	*i*-Pr	Et	78
6e	H	Me	Me	42

With the required propargylic alcohols in hand, we were then able to investigate the proposed Claisen rearrangement by condensation with a suitable α,α-disubstituted aldehyde. In the first instance a solution of propargylic alcohol **6e** and isobutyraldehyde (**11**) in toluene was heated at reflux for 24 hours in the presence of a substoichiometric amount of *para*-toluenesulfonic acid. Disappointingly, after concentration of the crude reaction mixture, no allene was observed in the crude ^1H and ^{13}C NMR spectra. Instead, lactone **14** was identified as the major product (Scheme 4). A plausible mechanistic rationale to account for the formation of the lactone **14** is shown in Scheme 4. Thus, the acid-catalysed condensation of alcohol **6e** and aldehyde **11** would, in the first instance give the hemiacetal **13**, which upon dehydration would provide the required intermediate propargyl vinyl ether **7a**. However, in competition with dehydration, cyclisation of hemiacetal **13** through an intramolecular transesterification reaction would give the lactone **14**. In order to circumvent this problem, it was anticipated that replacement of isobutyraldehyde with its dimethyl acetal would allow the reaction to proceed via a slightly different pathway, avoiding the problematic hemiacetal **13**. Thus, under acidic conditions, acetal **12** would undergo loss of a molar equivalent of methanol to give the oxonium ion, which upon reaction with propargylic alcohol **6e** would then provide the corresponding mixed acetal **15** which cannot readily undergo lactonisation. Elimination of methanol from mixed acetal **15** would then proceed to give propargyl vinyl ether **7a**, and consequently allene **8a** after [3,3]-sigmatropic rearrangement.

Table 2 Synthesis of Allenic Esters **8a–g** from Propargylic Alcohols **6a–d** and Acetals[8]

Alcohol	Acetal	Allene	Yield (%)
6e		 **8a**	40
6a		 **8b**	32
6c		 **8c**	44
6e		 **8d**	50
6b		 **8e**	24
6e		 **8f**	41
6d		 **8g**	45

Pleasingly, the reaction of acetal **12** with propargylic alcohol **6e** led to the formation of the expected allenic ester **8a**, which was isolated in 40% yield after purification by flash column chromatography. The reaction was then extended to a variety of propargylic alcohols **6a–d** and acetals to give a range of highly functionalised allenic esters **8a–g**,

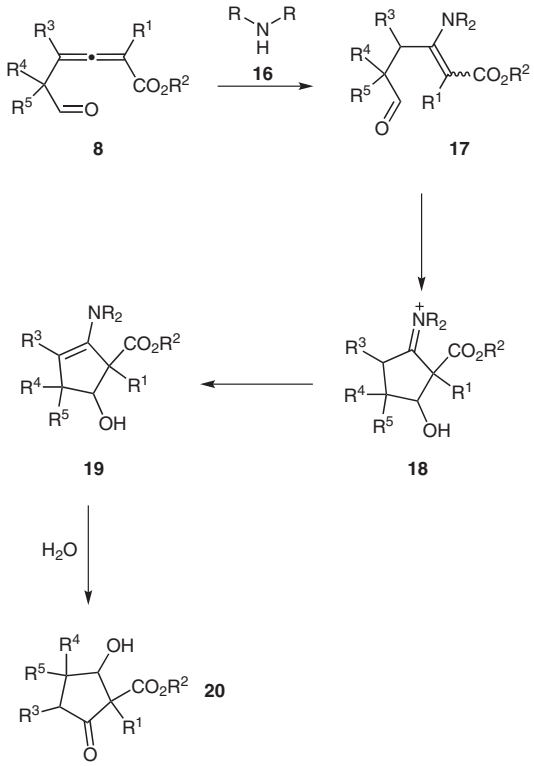


Scheme 4

all of which were stable towards column chromatography and storage (Table 2).

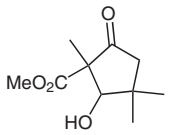
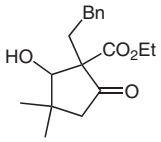
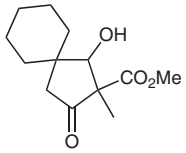
With a simple and robust route to the described allenic substrates in hand, a preliminary study into their synthetic potential was undertaken. The addition of primary and secondary amines to the central sp hybridised carbon atom of allenic esters allows for the regioselective preparation of synthetically versatile vinylogous urethanes under mild reaction conditions.[3,9] Within this framework, it was expected that the addition of secondary amines **16** to allenic esters **8a**–**g** would provide the corresponding vinylogous urethanes **17** which, upon 5-*exo* cyclisation onto the pendent carbonyl would give enamines **19** via intermediate iminium ions **18**. Hydrolysis of enamines **19** would then proceed to give substituted cyclopentanones **20** (Scheme 5).

Pleasingly, the reaction of trisubstituted allenic esters **8a**, **8c** and **8f** with pyrrolidine in acetonitrile at room temperature gave the expected cyclopentanones **20a**–**c** in moderate yields (Table 3). In all cases the cyclopentanones **20a**–**c** were formed as 1:1 mixtures of diastereoisomers. Disappointingly, the reaction of tetrasubstituted allenic esters **8b** and **8e** failed to provide the corresponding cyclopentanones. Only starting material was recovered from the reaction mixtures and attempts to effect the desired transformations at elevated reaction temperatures also failed, leading only to degradation of the starting material. Upon construction of molecular models of these highly substituted allenic esters it became apparent that a large level of steric crowding exits both above and below the plane of the molecule and, it is believed, that such steric constraints inhibit the approach of pyrrolidine to the central allenic carbon, preventing the desired cyclisation reaction from taking place.



Scheme 5

Table 3 Synthesis of Cyclopentanones **20a**–**c** from Allenic Esters **8**[10]

Allene	Cyclopentanone	Yield (%)
8a	 **20a**	45
8c	 **20b**	40
8f	 **20c**	67

In conclusion, we have shown that highly functionalised allenic esters can be readily assembled via an atom economical Claisen rearrangement of propargyl vinyl ethers, themselves obtained from simple acid-catalysed reactions

of suitably substituted propargylic alcohols and acetals. Preliminary experiments have clearly demonstrated that such substrates display significant potential for the synthesis of substituted cyclopentanones under mild reaction conditions. Reaction optimisation along with the development of both catalytic and stereoselective carbocyclisation reactions using these novel allenic substrates is currently underway in our laboratory.

Acknowledgment

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References and Notes

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(7) All pyruvic acid esters were purchased from the Aldrich chemical company.

(8) **General Experimental Procedure for the Synthesis of Allenic Esters 8a–g**: A solution of the propargylic alcohol (7.00 mmol), acetal (7.70 mmol) and PTSA (30 mg) in anhyd toluene (30 mL) in a flask fitted with a Dean and Stark separator was heated to a vigorous reflux for 24 h. The cooled solution was concentrated at reduced pressure and the crude oils were purified by flash column chromatography, eluting with PE–EtOAc (20:1) to give the described allenes **8a–g** as pale yellow oils. Data for **8f**: IR (thin film): 2933 (CH), 2804 (CH), 1957 (s, C=C=C), 1716 (C=O), 1450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.80 (m, 10 H, CH_2), 1.87 (d, *J* = 2.9 Hz, 3 H, Me), 3.72 (s, 3 H, OMe), 5.27 (q, *J* = 2.9 Hz, 1 H, CH), 9.32 (s, 1 H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7, 201.4, 167.7, 98.2, 95.7, 52.3, 51.5, 30.7, 30.6, 25.5, 22.0, 22.0, 15.0. HRMS: *m/z* [M + H] calcd for $C_{16}H_{18}O_3$: 223.13341; found: 223.13276.

(9) (a) Sugita, T.; Eida, M.; Ito, H.; Komatsu, N.; Abe, K.; Suama, M. *J. Org. Chem.* **1987**, *52*, 3789. (b) Sigman, M. S.; Eaton, B. E. *Tetrahedron Lett.* **1993**, *34*, 5367.

(10) **General Experimental Procedure for the Preparation of Cyclopentanones 20a–c**: Pyrrolidine (0.45 mmol) was added to a solution of the allenic ester (0.45 mmol) in MeCN (8 mL) at r.t. The solution was stirred at r.t. for 12 h and then concentrated at reduced pressure. The crude oil was dissolved in THF (10 mL) and 10% aq AcOH (10 mL) was added. The acidic solution was stirred at r.t. for 12 h and then the mixture was poured into sat. aq $NaHCO_3$ solution (10 mL). The aqueous phase was separated and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude oils were purified by flash column chromatography, eluting with PE–EtOAc (5:1) to give the title cyclopentanones **20a–c**. Data for **20c**: mp 34–36 °C. IR (Nujol): 3496 (br s, OH), 2929, 2856 (CH), 1747 (C=O, ketone), 1728 (C=O, ester), 1452 cm^{-1}. Diastereoisomer 1: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.74 [m, 10 H, $(CH_2)_5$], 1.47 (s, 3 H, Me), 2.27 (d, *J* = 18.4 Hz, 1 H, CH_2CO), 2.53 (br s, 1 H, OH), 2.82 (d, *J* = 18.4 Hz, 1 H, CH_2CO), 3.11 [s, 1 H, CH(OH)], 3.70 (s, 3 H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.7, 173.6, 77.9, 62.3, 54.2, 49.6, 42.5, 39.0, 29.4, 25.7, 24.3, 22.8, 22.3, 16.4. Diastereoisomer 2: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.75 [m, 10 H, $(CH_2)_5$], 1.33 (s, 3 H, Me), 2.18 (d, *J* = 5.6 Hz, 1 H, OH), 2.22 (d, *J* = 17.4 Hz, 1 H, CH_2CO), 2.59 (d, *J* = 17.4 Hz, 1 H, CH_2CO), 3.69 (s, 3 H, OMe), 4.39 [d, *J* = 5.4 Hz, 1 H, CH(OH)]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.3, 172.9, 85.9, 60.0, 52.8, 47.3, 42.2, 36.7, 29.0, 25.6, 23.3, 22.1, 15.6. HRMS: *m/z* [M + H] calcd for $C_{13}H_{20}O_4$: 241.14398; found: 241.14411.