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Intramolecular hetero Diels–Alder reactions of vinyl allenes and aldehydes☆

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Abstract—Compounds containing a vinyl allene moiety linked to an aldehyde by a tether have been synthesised and shown to undergo the intramolecular hetero Diels–Alder reaction. Only one compound with stereochemistry consistent with an *exo* approach of the dienophile to the dienic portion of the vinyl allene was obtained in each case. Depending on the length of the tether and on the substitution pattern on the allene the reactions were spontaneous at room temperature or required heating or the presence of a Lewis acid to proceed.

Vinyl allenes have been successfully used as dienes in the intramolecular Diels–Alder reaction leading to polycyclic compounds, which can be used to synthesise complex natural products.[1–4] A classification scheme has been suggested for these reactions based on the location of the tether on the vinyl allene.[5] Of all the possible types included in that classification, only two, Types I[1–3] and V_E[4] (Fig. 1), have been experimentally carried out, an important difference being observed between these two types in the stereochemical outcome of the reaction.

In Type V_E the system is more flexible and gives mixtures of compounds resulting from the *endo* or *exo* approach of the dienophile to the vinyl allene. In Type I systems, the structural features of the allene moiety confer a high degree of rigidity to the system, making the intramolecular Diels–Alder reaction of this type of compounds a highly selective process. The length of the tether also plays a role in the reactivity of the system.[5] In Type I systems, it was observed that when the bicyclic compound formed was of the hydrindane type, the reaction proceeded at room temperature or below depending on the substituents on the allene. When decalin-type systems were prepared, higher temperatures were required to effect the cyclization.

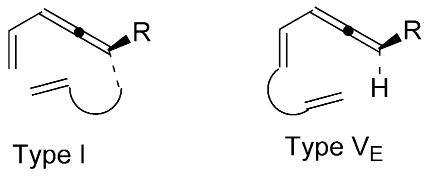

Figure 1.

We have recently shown that semicyclic vinyl allenes can act as dienes in the hetero Diels–Alder reaction with aldehydes as heterodienophiles in the presence of Lewis acids, and that the reactivity observed was similar to that of dienes substituted with alkoxy or silyloxy groups.[6]

Following our interest in the pericyclic reactivity of vinyl allenes, we decided to test the feasibility of carrying out the intramolecular variant of this reaction. Although only a few examples of intramolecular hetero Diels–Alder reactions in which the heterodienophile is a carbonyl compound exist,[7] we were intrigued by the effect of the allene on the reactivity. For this task, we needed to devise a procedure to prepare compounds containing the vinyl allene system with different substituents and an aldehyde group, linked by a tether of variable length. Based on the above considerations for the intramolecular Diels–Alder reaction of vinyl allenes, we decided to place the tether on the terminus of the

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Keywords: vinyl allene; intramolecular hetero Diels–Alder; cycloaddition.

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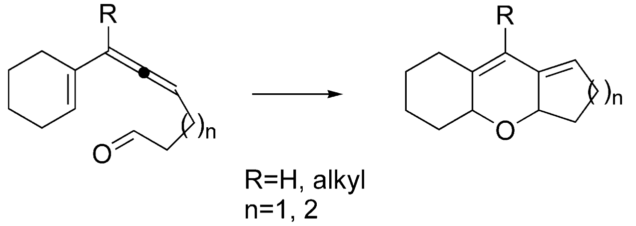
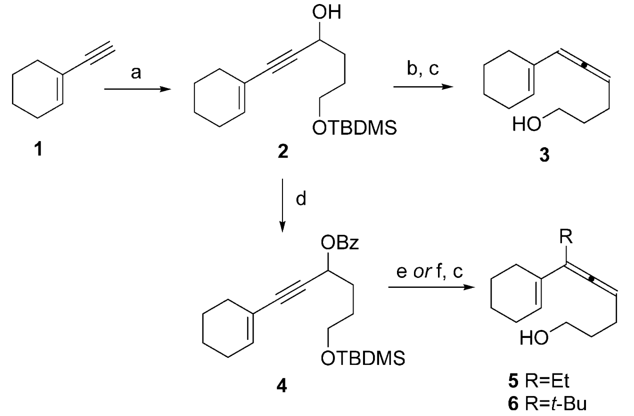


Scheme 1.



Scheme 2. *Reagents and conditions*: (Bz = COPh) (a) *n*-BuLi, −78°C, OHC$(CH_2)_3$OTBDMS, THF, 90%; (b) Ph_3P, DEAD, *o*-$NO_2C_6H_4SO_2NHNH_2$, THF, −15°C, 68%; (c) TBAF, THF, 97%; (d) *n*-BuLi, PhCOCl, −78°C, THF, 93%; (e) EtMgBr, CuBr·Me_2S, −60°C, THF, 44%; (f) *t*-BuLi, CuCN, −78°C, Et_2O, 46%.

allene (Type I), and devise a synthetic strategy that allowed us to introduce either a hydrogen or an alkyl group on the allene. Since different alkyl groups exert a similar electronic influence on cycloadditions and the differences in their roles are mainly steric,[8] we chose a simple alkyl group (methyl, ethyl) and a bulky one (*t*-butyl) for these studies. Thus, the required systems for our study were of the type shown in Scheme 1.

We started by studying the compounds with $n = 1$, which by similarity with the all-carbon version of the reaction, should be more reactive[5] and should yield an octahydro-cyclopenta[*b*]chromene system. The synthetic process for the preparation of those compounds is outlined in Scheme 2.

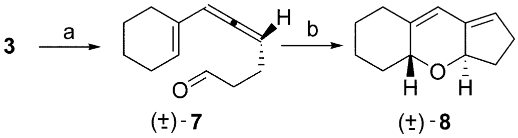
The propargyl alcohol **2** prepared by the addition of the lithium salt of 1-ethynylcyclohexene **1** to 4-*tert*-butyldimethylsilyloxybutanal[9] was treated with *o*-nitrobenzenesulfonylhydrazide (*o*-NBSH), DEAD and PPh_3 following Myers protocol[10] to give the vinyl allenol **3** after deprotection of the silyl group. Compound **2** was also transformed into the corresponding benzoate **4**, which was treated with different cuprates[11] to give, after a S_N2' reaction and deprotection, vinyl allenols **5** and **6**.

Compound **3** was converted in good yield into the aldehyde **7** required for the intramolecular hetero Diels–Alder reaction by a Swern oxidation (Scheme 3). This aldehyde **7** was then placed under the conditions developed for the intermolecular reaction of vinyl allenes and aldehydes,[6] that is, diethyl ether as solvent, $BF_3{\cdot}Et_2O$ as Lewis acid and room temperature. After 8 h of reaction followed by purification by flash column chromatography, tricyclic compound **8** was obtained in 18% yield.[12]

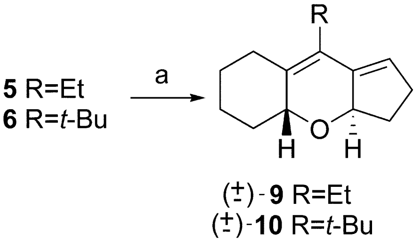
The structure of **8** was established by a combination of spectroscopic techniques,[13] and the relative stereochemistry shown in Scheme 3 was deducted from goesy experiments.[14] This structure is consistent with an intramolecular hetero Diels–Alder reaction in which the aldehyde has effected an *exo* approach to the dienic portion of the vinyl allene, which is the most feasible due to the constraints imposed by the allene and the length of the tether.

Although the yield obtained was disappointingly low, we had anticipated that compound **3** should be less reactive than **5** or **6**, since these two possess an alkyl substituent on the allene and in a position in which it can act as an activating group for the diene. In fact, when alcohol **5** was subjected to Swern oxidation under the same conditions used for **3**, no aldehyde was obtained after purification. Instead, the tricyclic system **9**, resulting from the intramolecular hetero Diels–Alder reaction, was isolated in a 67% yield (Scheme 4).

When the oxidation reaction was repeated keeping the temperature below rt during the workup, the corresponding aldehyde was observed as the major component in the crude reaction mixture by ^1H NMR spectroscopy. This aldehyde was converted into **9** upon standing in solution or when its purification was attempted by column chromatography.



Scheme 3. *Reagents and conditions*: (a) DMSO, $(COCl)_2$ −50°C, then Et_3N −50°C to rt (83%); (b) $BF_3{\cdot}Et_2O$, Et_2O, rt (18%).



Scheme 4. *Reagents and conditions*: (a) DMSO, $(COCl)_2$ −50°C, then Et_3N −50°C to rt (R = Et, 67%; R = *t*-Bu, 86%).

This result implies a very easy intramolecular hetero Diels–Alder reaction with an aldehyde as the heterodienophile, since it occurs at rt without the need of a Lewis acid.

A similar result was obtained when **6** was subjected to the same oxidising conditions, tricyclic compound **10** was isolated in an 86% yield. Again the corresponding aldehyde was observed in the crude reaction mixture prior to purification.

We then turned our attention to the homologous vinyl allenals containing one more carbon atom in the tether (compounds **11**–**13**, $n=2$, Scheme 1), which would yield octahydroxanthene-type products. The three compounds chosen were selected using the same criteria employed before, i.e. different and differently-sized substituents on the allene.

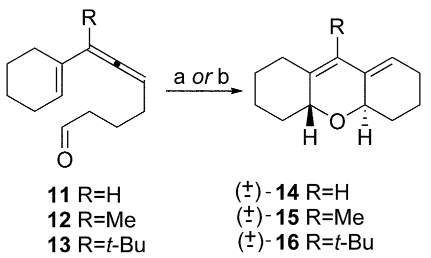
The preparation of vinyl allenols **11**–**13** was carried out following the same procedure shown in Scheme 2 using 5-*tert*-butyldimethylsilyloxypentanal[15] in the first step. The yields obtained were similar to those described for **3**, **5** and **6**.

No cyclization products were observed after purification of the oxidation reactions, which was expected based on the literature reports on the lower reactivity of the higher homologues in intramolecular Diels–Alder reactions. The aldehydes were unstable and thus had to be used immediately to avoid decomposition.

Under Lewis acid catalysis, only **12** and **13** yielded the expected cyclization products **15** and **16**, respectively, in moderate yields, whereas with **11** there was no reaction, only decomposition when longer reactions times were used (Scheme 5).

The easy transformation of **5** and **6** at room temperature led us to wonder whether their homologues **11**–**13** would react under strictly thermal conditions, and thus **11** and **12** were dissolved in toluene and heated to reflux. Under these conditions, **11** decomposed without any sign of transformation, whereas after 12 h, **12** afforded the tricyclic compound **15** in a 48% yield.

The structure and relative stereochemistry of these new tricyclic systems, deducted from goesy experiments,[14] follow the pattern found before, which implies an *exo* approach of the aldehyde to the diene.



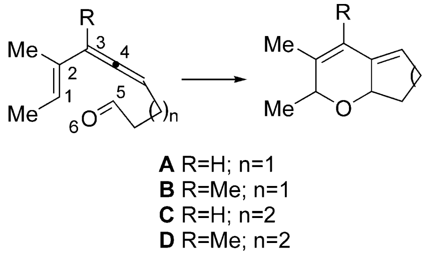
Scheme 5. *Reagents and conditions*: (a) Refluxing toluene, 12 h (R = Me, 48%); (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt (R = H, 0%; R = Me, 45%; R = *t*-Bu, 48%).

The behaviour of vinyl allenes in the intramolecular hetero Diels–Alder reaction is thus parallel to that of the all-carbon version of the reaction. The substituents on the allene act as activating groups facilitating the reaction, whereas the length of the tether plays an important role in the reactivity.[16]

The fact that several of the vinyl allenals used react under thermal conditions, at room temperature or higher, depending on the structure, without the need of a Lewis acid seems to point to a truly pericyclic mechanism as opposed to a cationic stepwise one. Although no experiments have been carried out to ascertain the mechanism involved, preliminary ab initio calculations on model systems[17] (Scheme 6) indicate, in the absence of Lewis acid, a concerted reaction with some degree of asynchronicity, which is greater in the alkyl substituted systems. Table 1 shows the calculated activation energy and the variation of bond index at the transition state (δB_i)[18] for the four models considered.

It can be observed that a good correlation exists between the calculated values for the activation energy on the models and the observed reactivity for the experimental counterparts. Model **B** (R = Me, $n=1$) is predicted to react more easily than **A** (R = H, $n=1$) and **D** (R = Me, $n=2$), and model **C** (R = H, $n=2$) is predicted to be the least reactive. Experimentally, compounds **5** and **6** (R = alkyl, $n=1$) react spontaneously at room temperature, **7** (R = H, $n=1$), **12** and **13** (R = alkyl, $n=2$) need Lewis acid activation and **11** (R = H, $n=2$) does not react under the conditions assayed.

The variation of bond indices indicates that, as expected for a hetero Diels–Alder reaction, in all cases



Scheme 6. Model compounds used in ab initio calculations. Arbitrary numbering.

Table 1. Activation energy, relative activation energy and variation of bond indices at the transition state for model systems calculated by ab initio methods[a]

Model	Ea (kcal/mol)	ΔEa (kcal/mol)	δB_{1-6}	δB_{4-5}
A	20.60	1.15	0.27	0.44
B	19.45	0.0	0.25	0.46
C	22.15	2.70	0.27	0.42
D	20.95	1.50	0.25	0.43

[a] B3LYP/6-31G(d)//B3LYP/6-31G(d) calculations. ZPVE scaled by 0.98 are included. For the arbitrary numbering, see Scheme 6.

there is some asynchronicity, with the carbon–carbon bond formed to a larger extent in the transition state (42–44%) than the carbon–oxygen bond (25–27%). The introduction of the methyl groups on the allene enhances this asynchronicity.

In conclusion, we have found that the intramolecular hetero Diels–Alder reaction of vinyl allenes with aldehydes can occur to give polycyclic compounds, provided that the right substitution pattern and length of tether are used. The reaction proceeds thermally, without Lewis acid, in several of the examples studied.

Acknowledgements

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12. Typical experimental procedure for the Lewis acid-catalysed reaction of vinyl allenals: To a solution of vinyl allenal **7** (100 mg, 0.57 mmol) in diethyl ether (20 mL) at 0°C, was added a solution of BF$_3$·Et$_2$O (0.08 mL, 0.63 mmol) in diethyl ether (2 mL). The reaction was stirred overnight and then Et$_3$N (1 mL) was added followed by water. The reaction was extracted with diethyl ether (3×15 mL), dried and concentrated. After flash column chromatography (3% EtOAc in hexanes), **8** was obtained as a clear oil (18 mg, 18%). ^{1}H NMR (400 MHz, C$_6$D$_6$) δ 6.11 (s, 1H), 5.44 (s, 1H), 4.71 (t, J = 7.0 Hz, 1H), 4.23 (dd, J = 4.5, 11.9 Hz, 1H), 2.27–2.32 (m, 3H), 2.14–2.16 (m, 1H), 1.99–1.79 (m, 4H), 1.58–1.64 (m, 2H), 1.08–1.22 (m, 2H); ^{13}C NMR (100 MHz, C$_6$D$_6$) δ 144.5, 139.5, 121.0, 113.9, 77.0, 76.1, 34.5, 33.6, 31.2, 30.0, 28.3, 25.1; HRMS (EI) *m*/*z* calcd for C$_{12}$H$_{16}$O 176.1201, found 176.1205.
13. All new compounds reported exhibit spectroscopic data (^{1}H and ^{13}C NMR, COSY, HSQC and HMBC) consistent with the proposed structures.
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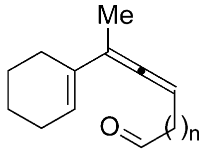
16. Other vinyl allenals **17** and **18** with a one carbon atom shorter and longer tether, respectively, than those studied in this work were also prepared following the same strategy and subjected to the same reaction conditions. As expected from the literature data neither one reacted to give cyclization products.[5]



17 n=1
18 n=4

17. Ab initio calculations were carried out with the Gaussian 98W suite of programs. Gaussian 98 (Revision A.6), Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1998.
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