Competition between Alkenes in Intramolecular Ketene–Alkene [2 + 2] Cycloaddition: What Does It Take to Win?

Guillaume Bélanger,* François Lévesque, Julie Paquet, and Guillaume Barbe

Laboratoire de synthèse organique et de développement de stratégies de synthèse, Département de Chimie, Université de Sherbrooke, 2500 boulevard Université, Sherbrooke, Québec J1K 2R1, Canada

guillaume.belanger@usherbrooke.ca

Received September 17, 2004

In the course of developing a new synthetic methodology using ketenes in sequential cycloaddition steps, we were faced with a competition problem with molecules containing a ketene tethered to more than one reacting partner. To pinpoint the electronic and tethering requirements for a chemoselective reaction, we undertook a series of ketene–alkene [2 + 2] cycloaddition competition experiments. Those experiments were conducted on molecules containing either two identical alkenes having different tether lengths or two alkenes having the same tether length but being electronically different. We demonstrated that the reaction is much faster for forming five-membered rings than six-membered rings and calculated the Hammett constant $\rho$ for intramolecular ketene–alkene [2 + 2] cycloadditions to be $-1.39$.

Introduction

Since their first preparation in 1905,1 ketenes have been widely studied due to their unique reactivity. Many different ketene–alkene [2 + 2] cycloaddition mechanisms have been proposed,2 and nowadays, two of them are commonly accepted: a stepwise mechanism involving sequential nucleophilic additions via a zwitterionic intermediate3 and a concerted cycloaddition. The latter is an antarafacial process, thermally allowed according to the frontier molecular orbital (FMO) theory,4 and could be highly asynchronous.2,5 It is also suggested that these two mechanisms may compete, depending on the nature of the alkene reacting with the ketene.2,5

As we were developing a new synthetic strategy using ketenes in sequential cycloaddition steps, we faced with a competition issue with molecules containing a ketene tethered to more than one reacting partner. To pinpoint the electronic and tethering requirements for a chemoselective reaction, we undertook a series of ketene–alkene [2 + 2] cycloaddition competition experiments. Those experiments were conducted on molecules containing either two identical alkenes having different tether lengths or two alkenes having the same tether length but being electronically different. We demonstrated that the reaction is much faster for forming five-membered rings than six-membered rings and calculated the Hammett constant $\rho$ for intramolecular ketene–alkene [2 + 2] cycloadditions to be $-1.39$.

tatively assess the ring size effect on the relative cycloaddition rates. Second, it is known that ketenes are electron deficient and react preferentially with electron-rich alkenes, as was nicely demonstrated in ketene [2 + 2] cycloadditions with various para-substituted styrenes.\(^8\) However, this is the only study of the influence of the electronic character of alkenes in [2 + 2] cycloadditions involving ketenes, and the interpretation of the results was neither conclusive nor quantitative.\(^9\) Because this information is crucial to us in order to develop our synthetic methodology, we decided to run a series of ketene–alkene [2 + 2] cycloaddition competition experiments. The results presented herein are divided into two main parts: the study of the influence of the tether length and the study of the influence of the electronic character of alkenes in intramolecular [2 + 2] cycloadditions with ketenes.

### Results and Discussion

#### Study of the Influence of the Tether Length between a Ketene and an Alkene in Intramolecular [2 + 2] Cycloadditions

We chose substrates containing identical alkenes attached to the ketene with different tether lengths. The synthesis of the first model compound is described in Scheme 2. An alkylation of the dianion of hept-6-enoic acid (1) with 6-iodohex-1-ene gave the branched acid 2 (61% yield).\(^{10}\) The latter was then treated with oxalyl chloride in refluxing toluene, and the resulting acyl chloride 3 was clean and was used without purification for the generation of ketene 4 by deprotonation with triethylamine in refluxing toluene. This was followed by an in situ [2 + 2] cycloaddition. We were pleased to obtain only one product (>95:5 by 1H NMR analysis of the crude material) in excellent yield (82%).

At that point, spectral analysis could not tell us which of the two possible adducts (5 or 6) was preferentially formed. To determine the identity of the cycloadduct, we independently prepared both the [3.2.0] and the [4.2.0] bicyclic adducts. On one hand, the synthesis of 8 was accomplished in three steps, starting with the alkylation of 1 with 1-iodohexane (60% yield, Scheme 3). The ketene was prepared from the corresponding acyl chloride and gave the bicyclo[3.2.0]heptanone 8 in 86% yield.

On the other hand, the bicyclo[4.2.0]octanone 11 was prepared from ethyl heptanoic acid (9; Scheme 4) using exactly the same reactions as described in Scheme 2. We were delighted to observe that the methylene next to the carbonyl of 11 had measurably different chemical shifts and coupling constants for its protons compared to those of compound 8 (Scheme 3).
We then reduced the alkene of the crude material (5 or 6) obtained from the competition experiment (Scheme 2), and the product obtained gave an NMR spectrum that matched perfectly that of compound 8. This result confirmed that the adduct 5 was the only product obtained from the competition experiment, thus showing a strong dependence of the intramolecular ketene formation on the steric hindrance of the substituent on a remote position, separated from the multiple bond correlation and gives long-range $^1H$ coupling, typically over three to four bonds. (b) HSQC stands for heteronuclear single quantum correlation and gives $^1H$-$^13C$ coupling over one bond. (c) HMBC stands for heteronuclear multiple bond correlation and gives long-range $^1H$-$^13C$ coupling, typically over two to three bonds.

TABLE 1. NMR Data of Possible Adducts 19

<table>
<thead>
<tr>
<th>position</th>
<th>$\delta$ (ppm)</th>
<th>multiplicity</th>
<th>J (Hz)</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.04</td>
<td>s</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>3.16</td>
<td>t</td>
<td>3.5</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>2.45 (eq)</td>
<td>m</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>2.45 (ax)</td>
<td>m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.70 (eq)</td>
<td>dqm&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.5, 8.5</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>1.90 (ax)</td>
<td>m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.25 (eq)</td>
<td>ddd</td>
<td>13.0, 8.5, 4.0</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>2.45 (ax)</td>
<td>m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1.12</td>
<td>td</td>
<td>13.0, 3.5</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>1.28</td>
<td>td</td>
<td>13.0, 4.5</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.22</td>
<td>m</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>12</td>
<td>1.85</td>
<td>m</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>1.95</td>
<td>sept&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>5.90</td>
<td>dt</td>
<td>16.0, 7.0</td>
<td>130</td>
</tr>
<tr>
<td>15</td>
<td>6.20</td>
<td>d</td>
<td>16.0</td>
<td>130</td>
</tr>
</tbody>
</table>

<sup>a</sup> Doublet of quintets. <sup>b</sup> Septuplet.

(11) Only the intermolecular version has been reported. 8 Pot Knoevenagel condensation–hydroboration reaction. This procedure constitutes an efficient way to synthesize monoalkylated dicarbonyls. 13 The resulting diester 13 was then transesterified and decarboxylated in ethanol using microwaves at 170 °C. The stereochemical integrity of the alkene was preserved. 14 After a DIBALH reduction of the ester 14 in 98% yield, the resulting alcohol 15 was iodinated (89% yield) and then doubly alkylated on Meldrum’s acid in 47% yield using cesium carbonate. A microwave-assisted hydrolysis–decarboxylation of 16 cleanly generated the corresponding monoaic 17, which was transformed into the desired cycloadduct 19 (or 18) via the acyl chloride and ketene intermediates.

Finding suitable proton signals in the $^1H$ NMR spectrum to use in the determination of product ratios was not easy, since the vinylic proton signals were overlapping with unreacted starting material and/or with an anhydride side product. 15 The assignments of proton and carbon signals in adduct 19 (or 18) were accomplished using $^1H$, COSY, NOESY, TOCSY, 16a HSQC, 16b and HMBC<sup>13c</sup> and are gathered in Table 1. From a portion of


(14) For cis alkenes, used in other sequences of reactions that are not mentioned in this paper, this step gave partial isomerization.

(15) Even with careful manipulations, traces of water could generate an anhydride from two molecules of acyl chloride. The formation of anhydride occurs during the ketene formation step, when the acyl chloride is heated in the presence of triethylamine. The acyl chloride formation itself is clean and usually quantitative. The amount of anhydride observed is greater when the alkenes are deactivated toward the [2 + 2] cycloaddition with the ketene.

(16) (a) TOCSY stands for total correlation spectroscopy and gives long-range $^1H$-$^1H$ coupling, typically over three to four bonds. (b) HSQC stands for heteronuclear single quantum correlation and gives $^1H$-$^13C$ coupling over one bond. (c) HMBC stands for heteronuclear multiple bond correlation and gives long-range $^1H$-$^13C$ coupling, typically over two to three bonds.
the HMBC spectrum, three pieces of evidence allowed us to unambiguously assign the structure as being 19.\(^{(17)}\)

Moreover, from the \(^1\)H NMR spectrum of 19, we identified two characteristic signals of the cycloadduct: the 3.16 ppm triplet and the 3.04 ppm singlet, corresponding to H2 and H1, respectively. These peaks are clearly identifiable in the crude mixture of the reaction. This information proved crucial for ratio determination in the following competition experiments.

With the structure of the cycloaddition product 19 secured, we then undertook the construction of a series of substrates, depicted in Figure 1. We selected five aryl substituents (X: methoxy, methyl, chloro, trifluoromethyl, and nitro) that would enable us to generate a standard Hammett plot and determine the \(\alpha_p\) constant of the reaction. The syntheses of the substrates are depicted in Schemes 6 and 7. The alcohol 15 was oxidized using Swern's conditions, and then the monobranched Meldrum's acid 20 was prepared using the usual Knoevenagel-hydroboration procedure (Scheme 6).

The para-substituted aryls were introduced by a Suzuki coupling between the vinylic boronate 21 and the appropriate aryl iodide followed by a hydrochloric acid cleavage of the silyl ether in the workup (Scheme 7). The resulting para-substituted styrenes 22a–e were iodinated in good yields and alkylated on 20. The Meldrum's acid moiety was then hydrolyzed and decarboxylated to the corresponding carboxylic acids 23a–e. The latter were transformed into the acyl chlorides followed by a triethylamine treatment to generate the ketenes in situ, which underwent the \([2+2]\) cycloaddition. Mixtures of 24a–e and 25a–e were obtained, depending on the nature of the X substituent on the aryl.

It is reasonable to think that the \(^1\)H NMR chemical shifts for the H1 singlet and H2 triplet of 25 should be nearly the same on going from X = OMe (25a) to X = NO2 (25e), as these groups are far from the bicyclic core. This is exactly what we observed (Figure 2).

The product ratios (24:25) were derived from these crude \(^1\)H NMR spectra (Figure 2). The integration of the H1 singlets on both 24 and 25 gave a ratio that matched perfectly that obtained from the integration of the H2 triplets of 24 and 25. The average ratio from the integrated singlets and triplets as well as the reported \(\alpha_p\) values\(^{(19)}\) for every X substituent are given in Table 2.

\(^{17}\) The spectral evidence that allowed us to assign the structure as being 19 is discussed in detail in the Supporting Information, section V.


---

**FIGURE 2.** Crude cycloadduct \(^1\)H NMR spectra.

**TABLE 2.** Ratios of Cycloadducts 24a–e and 25a–e

<table>
<thead>
<tr>
<th>X</th>
<th>24:25</th>
<th>(\alpha_p) value(^{(19)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe (a)</td>
<td>3.2:1.0</td>
<td>-0.27</td>
</tr>
<tr>
<td>Me (b)</td>
<td>2.4:1.0</td>
<td>-0.17</td>
</tr>
<tr>
<td>Cl (c)</td>
<td>1.0:1.3</td>
<td>0.23</td>
</tr>
<tr>
<td>CF3 (d)</td>
<td>1.0:4.1(^{(b)})</td>
<td>0.54</td>
</tr>
<tr>
<td>NO2 (e)</td>
<td>1.0:9.0(^{(c)})</td>
<td>0.78</td>
</tr>
</tbody>
</table>

\(^{(a)}\) Ratios determined from the average of the integration of H1 singlets and integration of H2 triplets. \(^{(b)}\) The H1 singlets of 24d and 25d are overlapping. \(^{(c)}\) The H1 and H2 signals of 24e, as well as the H2 triplet of 25e, are all in the same multiplet (3.19–3.13 ppm).
in toluene, from competition experiments between phenyl-substituted alkenes and alkenes bearing a para-substituted aryl. Having a negative sign of the ρ value means that the reaction is accelerated by electron-donating groups, which is in accordance with reported data. The absolute ρ value of 1.39 is the first clear and quantified indication of a modest charge development at the transition state, stabilized by electron-donating groups on the styrene, for [2 + 2] cycloadditions with a tethered ketene. The Hammett plot also serves as an extremely useful prediction tool that will be crucial for the development of our synthetic strategy using cascades of ketene cycloadditions, as well as for any reacting partner of known ρ value.

**Experimental Section**

(5E)-1-(Hex-5′-enyl)bicyclo[3.2.0]heptan-7-one (5). A solution of carboxylic acid 2 (400 mg, 1.9 mmol) in toluene (2.0 mL) was placed in a tube under argon. Oxalyl chloride (830 μL, 9.5 mmol) was added at room temperature, and the tube was sealed, heated to 120 °C for 2 h in an oil bath, and then cooled to room temperature and opened. The solution was concentrated under mechanical pump vacuum. The crude acyl chloride 3 was dissolved in toluene (33 mL), and Et3N (1.6 mL, 11.4 mmol) was added at room temperature. The tube was sealed, heated to 120 °C overnight, cooled to room temperature, and opened. Saturated aqueous NH4Cl was added, and the biphasic mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated. The crude material was purified by flash chromatography (19:1 hexanes–EtOAc) to give 300 mg (82%) of pure 5 as a colorless oil: 1H NMR (300 MHz, CDCl3) δ 5.69 (d, J = 17.0, 10.6, 6.5 Hz, 1H), 4.90 (dd, J = 17.5, 1.5 Hz, 1H), 4.84 (d, J = 11.5 Hz, 1H), 3.01 (dd, J = 18.0, 9.5 Hz, 1H), 2.49–2.44 (m, 1H), 2.33 (dd, J = 18.0, 4.5 Hz, 1H), 1.99–1.87 (m, 4H), 1.78–1.15 (m, 10H); 13C NMR (75 MHz, CDCl3) δ 217.8, 138.6, 114.3, 75.8, 49.1, 35.8, 38.8, 33.5, 32.9, 32.6, 29.3, 25.0, 24.9; IR (film) ν3077, 2935, 2865, 1774, 1068, 964 cm⁻¹; MS (ESI) m/z 192 (15) [M⁺], 150 (100), 135 (70), 121 (91), 108 (71); HRMS (EI) m/z calcd for C15H20NO4 192.1514, found 192.1519.

(5E)-2,2-Dimethyl-5-(3′-phenylallyl)-1,3-dioxane-4,6-dione (19). Meldrum’s acid (9.51 g, 66.0 mmol) was added to a solution of BH3·SMe2 complex (288 g, 65.9 mmol) in MeOH (60 mL) at room temperature in a water bath. trans-Cinnamaldehyde (12; 8.32 mL, 66.0 mmol) was then added dropwise (exothermic). After 3 h at room temperature, H2O (160 mL) was added (a white precipitate was formed) followed by 3 N HCl (240 mL). The suspension was stirred overnight and then was filtered and dried under vacuum over P2O5 to afford 12.1 g (71%) of pure 13 as a white solid: 1H NMR (300 MHz, CDCl3) δ 7.36–7.19 (m, 5H), 6.61 (d, J = 15.5 Hz, 1H), 6.26 (dd, J = 15.5, 7.5 Hz, 1H), 3.66 (t, J = 5.0 Hz, 1H), 3.06–3.01 (m, 2H), 1.79 (s, 3H), 1.75 (s, 3H); HRMS (EI) calcd for C17H15NO4 (MNH⁺) 278.1392, found 278.1386.

(4E)-Ethyl 5-Phenylpent-4-enolate (14). A solution of 13 (270 g, 10.4 mmol) in EtOH (22 mL) was placed in a sealed tube and heated to 170 °C for 1.5 h in a microwave oven. The tube was then cooled to room temperature and opened, and the solution was transferred to a round-bottom flask. Silica gel was added, and the slush was concentrated under reduced pressure. The resulting crude material adsorbed on silica gel was loaded directly on a column and was purified by flash chromatography (19:1 hexanes–EtOAc) to give 1.9 g (90%) of pure 14 as a colorless oil: 1H NMR (300 MHz, CDCl3) δ 7.36–7.17 (m, 5H), 6.43 (d, J = 16.0 Hz, 1H), 6.21 (dt, J = 16.0, 6.5 Hz, 1H), 5.56 (d, J = 10.5 Hz, 1H), 4.66 (t, J = 6.0 Hz, 2H), 2.96 (s, 3H), 2.12 (s, 3H), 1.95 (s, 3H); HRMS (EI) calcd for C21H20NO2 (M+H+) 322.1466, found 322.1474.

The characterization is identical with that reported for the same compound, but prepared through another route. See: Prat, M.; Moreno-Mañas, M.; Ribas, J. Tetrahedron 1988, 44, 7205–7212.

(20) The 1H NMR spectrum of 24d with Ph = CF3C6H4 (i.e. with two ρ-CF3-styrene branches) prepared independently showed an H1 singlet at 3.11 ppm and an H3 triplet at 3.18 ppm.

(21) See the 1H NMR spectra of isolated and purified 24e and 25e in the Supporting Information.

(22) As an indication of the difference in reaction rates between an intramolecular and an intermolecular reaction, 4-bromobutyl-1-amine cyclizes in a five-membered ring 10⁶ times faster than the dimerization rate in a 1 M solution (Sirelowski, A., Jr, Solvolysis Displacement Reactions; McGraw-Hill: New York, 1962; p 105), or 200 000 times faster in a 0.505 M solution. Although the folding of the molecule for this 5-exo-tet cyclization is not the same as for the [2 + 2] cycloaddition, it is nonetheless an indication that the intramolecular reaction should be negligible.


(24) As a criterion of linearity, the correlation coefficient r is required to be at least 0.95 and preferably above 0.98. See: Connors, K. A. Chemical Kinetics: VCH: New York, 1990; pp 310–320.

(25) For reactions that do not follow the same mechanism depending on the nature (electron withdrawing or electron donating) of the substrate (alkene in this case), a change of slope is usually observed in the ρ vs log(k/k0) graph.

**Figure 3.** Hammett plot for [2 + 2] cycloaddition.
Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 2.60–2.34 (m, 4H), 1.24 (t, J = 7.0 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ 172.5, 137.1, 130.7, 128.1, 126.8, 125.9, 59.9, 33.6, 28.0, 13.9; MS (EI) m/z 204 (29) [M+], 130 (100), 117 (69), 91 (126); HRMS (EI) m/z calculated for C11H13I2 272.0069, found 272.0062. 


Supporting Information Available: Text giving experimental procedures for compounds 2, 7, 8, 10, 11, 15, 20, and 22–25, figures giving 1H and 13C NMR spectra for compounds 2, 5, 7, 8, 10, 11, 13–17, 19, 20, and 22–25, and figures giving COSY, NOESY, TOCSY, HMQC, and HMBC spectra for 19. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0483466