Regioselectivity of the Intramolecular Photocycloaddition of α,β-Butenolides to a Terminal Alkene

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Abstract: The intramolecular [2+2] photocycloaddition of α,β-buteno- lides to a terminal double bond tethered to the lactone through the γ-position and located at a suitable distance has been studied. The regioselectivity of the photoisomerization depends on the substitution pattern of the substrate and can be rationalized by simple theoretical calculations performed on the diradical intermediates.

Key words: intramolecular photochemical cycloaddition, α,β-buteno- lides, alkenes, regioselectivity, intermediate diradicals

Since the first published studies dealing with the [2+2] photocycloaddition of enones to alkenes,1–3 this reaction has found broad application in the synthesis of natural products as a key step in the preparation of many target molecules containing a cyclobutane ring in their skeleton.4–7 Nevertheless, reports on the use of α,β-unsaturated lactones as substrates for [2+2] photocycloadditions are quite limited.8–16 The synthetic utility of these reactions relies on both the regio- and stereoselectivity of the process. Studies addressed to the issue of facial diastereoselectivity in the intramolecular photocycloadditions to chiral lactones have been performed11,13–15 and, as a result, successful stereoselective syntheses of (+)- and (−)-bourbonene13 and (+)- and (−)-grandisol11,14b,15c,f have been developed.

The light induced intramolecular [2+2] cycloaddition of an enone containing an additional carbon–carbon double bond was first observed for L-carvone.17,18 More recently, new examples have been reported,19–22 in which the main purpose is to understand, and eventually to control, the regio-chemistry of the products. For intramolecular processes, on the basis of experimental results, it seems to be a preference for the initial formation of a five-membered ring (rule of five),21,30,31 although the regioselectivity may be strongly affected by electronic as well as steric factors.

To evaluate the influence of the substituents at the α and β positions on the regioselectivity of the intramolecular [2+2] cycloaddition of butenolides analogous to 2, we decided to synthesize compounds 4–6 (Scheme 2) and investigate their photochemical isomerization.

Butenolides 4 and 6 were prepared through a three step sequence of reactions32 condensation of 1,2-epoxyhex-5-ene (3) with the dianion of phenylselenoacetic or 2-phe-
nylselenopropionic acid, respectively, acid induced lactonization, and oxidation of the selenide function with consequent thermal elimination. Total yields were 95% for 4 and 57% for 6. Introduction of a methyl group at the \( \beta \)-carbonyl position of 4 by treatment with diazomethane followed by pyrolysis of the corresponding pyrazoline afforded 5 in 69% overall yield.

Preliminary irradiation experiments were performed on a Rayonet® system at room temperature (Table 1). Degassed solutions of lactone 4 were irradiated at 254 nm (run 1), 300 nm (run 2) and 350 nm (run 3) until full conversion of the substrate. Purification by flash column chromatography gave in all three cases a ca 3:1 mixture of the regioisomers 7a and 7b (Scheme 3), although the isolated ratio of these isomers is not a reliable measure of the regioselectivity of the cycloaddition due to the high volatility of isomer 7a (see below). We were unable to separate compounds 7a and 7b, but GC/MS analysis showed that both reaction products had the same molecular weight as the starting butenolide 4. The structure of each isomer was assigned by \( ^1 \text{H} \) and \( ^{13} \text{C} \) NMR analysis of enriched samples with the help of DEPT, COSY and \( ^1 \text{H}/^{13} \text{C} \) correlation experiments. For the major isomer, it was observed that the \( \beta \)-carbonyl proton in the lactone ring was bonded to three different methine groups, a fact which is compatible with H-8 in 7a, but not with H-9 in 7b.

Since the irradiation of acetone solutions gave cleaner crude reaction products and the regioselectivity of the cycloaddition did not seem to be affected by the irradiation frequency, the next experiments with substrates 5 and 6 were performed under the conditions of run 2. Irradiation of 5 (run 4) took 8 hours to reach full conversion and, after flash column chromatography, afforded a 7:1 mixture of 8a and 8b in 50% yield. Again we were unable to separate this mixture, but the structures were assigned by GC/MS analysis and NMR experiments as above. Irradiation of 6 (run 5) for 5 hours allowed the isolation of a 1.6:1 mixture of 9a and 9b in 58% yield. The structure of each isomer was elucidated by GC/MS and NMR analyses of enriched mixtures as in the precedent cases. Tables 2 and 3 summarize the most significant \( ^1 \text{H} \) and \( ^{13} \text{C} \) NMR data observed for compounds 7–9.

Next, the experiments were repeated in a photochemical reactor using a 125 W medium pressure mercury lamp, fitted in an immersion Pyrex® cooling jacket, with a careful control of the internal temperature (entries 6–10). For these runs, the regioisomeric ratio was determined through GC analysis of the reaction mixture and it is therefore representative of the regioselectivity of the cycloaddition. It was observed that the regioselectivity was independent of the reaction temperature (compare entries 6, 7 and 8). An experiment parallel to run 7 with a four-fold diluted solution also gave the same regioisomeric ratio. The straight (head to head) regioisomer always predominates, but the proportion of the crossed (head to tail)
In Table 4.

energ conformation of the alternative intermediates

acycloadduct increases substantially when the starting
butenolide bears a methyl group at the \( \alpha \)-carbonyl position and it diminishes slightly when the methyl group is at the \( \beta \)-carbonyl position.

To explain the regioselectivity of these reactions, the intermediate diradicals leading to each product have to be considered. For intermolecular [2+2] photocycloadditions of enones to monosubstituted olefins, attack at the less substituted terminus of the olefin is supposed to occur in the first place\(^1\), but for intramolecular processes steric constraints may have a decisive influence on the regioselectivity.\(^2\) It has been demonstrated that simple molecular mechanics calculations may be used to analyze the geometry of diradical species and inter-radical distances (IRD) minor than 3 Å are considered appropriate for ring closing.\(^3\) We have calculated the relative stability and geometry of the four possible intermediate diradicals, I–IV, for each irradiated substrate (Figure, Table 4). Molecular mechanics (MMFF94) was used for assigning the lowest energy conformer to each intermediate species and its equilibrium geometry was then optimized applying the semi-empirical AM1 model. The results are summarized in Table 4.

Table 2 \( ^1H \) and \( ^13C \) NMR Data of Compounds 7a–9a.\(^{\delta} \), J (Hz)

<table>
<thead>
<tr>
<th>Product</th>
<th>H-1</th>
<th>H-4</th>
<th>H-8</th>
<th>C-1</th>
<th>C-4</th>
<th>C-7</th>
<th>C-8</th>
<th>C-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>3.02 (m)</td>
<td>5.02 (dd, ( J_{4,6} = 6.6 ), ( J_{4,5} = 4.1 ))</td>
<td>3.30 (q, ( J_{4,5} = J_{4,7} = 7.1 ))</td>
<td>36.4</td>
<td>86.5</td>
<td>36.0</td>
<td>44.7</td>
<td>31.6</td>
</tr>
<tr>
<td>8a</td>
<td>= 2.7</td>
<td>4.53 (d, ( J_{4,5} = 2.8 ))</td>
<td>-</td>
<td>41.3</td>
<td>91.6</td>
<td>41.5</td>
<td>52.7</td>
<td>28.2</td>
</tr>
<tr>
<td>9a</td>
<td>-</td>
<td>4.96 (ddd, ( J_{4,5} = 7.2 ), ( J_{4,5} = 4.3 ), 1.5)</td>
<td>2.98 (br t, ( J_{4,5} = J_{4,7} = 7.2 ))</td>
<td>50.1</td>
<td>84.6</td>
<td>32.2</td>
<td>50.2</td>
<td>39.2</td>
</tr>
</tbody>
</table>

Table 3 \( ^1H \) and \( ^13C \) NMR Data of Compounds 7b–9b.\(^{\delta} \), J (Hz)

<table>
<thead>
<tr>
<th>Product</th>
<th>H-1</th>
<th>H-4</th>
<th>H-8</th>
<th>C-1</th>
<th>C-4</th>
<th>C-7</th>
<th>C-8</th>
<th>C-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>2.96 (t, ( J_{4,5} = J_{4,6} = 6.1 ))</td>
<td>-</td>
<td>3.09 (dq, ( J = 7.1 ), ( J = 5.6 ))</td>
<td>46.2</td>
<td>82.3</td>
<td>37.3</td>
<td>24.5–23.1</td>
<td>40.9</td>
</tr>
<tr>
<td>b</td>
<td>2.63 (d, ( J = 7.0 ))</td>
<td>4.60 (br t, ( J_{4,5} = 2.2 ))</td>
<td>-</td>
<td>51.4</td>
<td>87.9</td>
<td>34.0</td>
<td>30.0</td>
<td>-</td>
</tr>
<tr>
<td>b</td>
<td>-</td>
<td>4.99 (br d, ( J = 7.0 ))</td>
<td>2.70 (m)</td>
<td>42.1</td>
<td>81.3</td>
<td>43.1</td>
<td>23.4</td>
<td>44.2</td>
</tr>
</tbody>
</table>

Table 4 Geometrical Data for the Minimum Energy Conformation of Intermediate Diradicals I–IV

<table>
<thead>
<tr>
<th>Diradicals</th>
<th>( R_a )</th>
<th>( R_p )</th>
<th>Energy (kcal mol(^{-1}))</th>
<th>IRD (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( I_9/|I_8 )</td>
<td>H</td>
<td>H</td>
<td>19.3/78.9</td>
<td>2.7/2.8</td>
</tr>
<tr>
<td>( I_9/|II_8 )</td>
<td>H</td>
<td>CH(_3)</td>
<td>20.8/84.8</td>
<td>2.8/2.8</td>
</tr>
<tr>
<td>( I_9/II_9 )</td>
<td>CH(_3)</td>
<td>H</td>
<td>25.0/81.3</td>
<td>2.7/2.9</td>
</tr>
<tr>
<td>( III_{9b}/IV_{7b} )</td>
<td>H</td>
<td>H</td>
<td>35.1/67.9</td>
<td>2.9/3.8</td>
</tr>
<tr>
<td>( III_{9b}/IV_{9b} )</td>
<td>H</td>
<td>CH(_3)</td>
<td>36.5/74.8</td>
<td>3.0/3.8</td>
</tr>
<tr>
<td>( III_{9b}/IV_{9b} )</td>
<td>CH(_3)</td>
<td>H</td>
<td>37.8/70.0</td>
<td>2.9/3.8</td>
</tr>
</tbody>
</table>

\(^a\) The calculations were performed using the PC SPARTAN pro program of Wavefunction, Inc.
\(^b\) Energy of the most stable conformer (MMFF94).
\(^c\) Inter-radical distance (IRD) in the most stable conformer (AM1).

\( ^1H \) and \( ^13C \) NMR Data of Compounds 7a–9a.\(^{\delta} \), J (Hz)

Regarding the two kind of diradicals leading to the straight adducts 7a–9a, those of type I, coming from initial collapse of the enone \( \alpha \)-carbon with the olefin terminal position, gave lower energies than those of type II, in which the initial bond is formed between the enone \( \beta \)-car-

Figure Structures of intermediate diradicals I–IV

The calculations were performed using the PC SPARTAN pro program of Wavefunction, Inc.

Energy of the most stable conformer (MMFF94).

Inter-radical distance (IRD) in the most stable conformer (AM1).
In conclusion, the regioselectivity of the intramolecular [2+2] photocycloaddition of $\alpha,\beta$-butenolides to a terminal double bond located at a suitable distance depends on the substitution pattern of the substrate. Very simple theoretical calculations performed on the diradical intermediates, considering the relative energy and inter-radical distance of the most stable conformer, are in good qualitative agreement with the experimental regioselectivity.

All solvents were purified and dried by standard techniques just before use. Diisopropylamine was freshly distilled over NaOH. Phenylselenoacetic acid and 2-phenylselenopropionic acids were prepared following previously described procedures. Photochemical reactions at r.t. were performed on a Rayonet reactor and at 0°C using a Kugelrohr (70–75°C, oven temp./0.06 Torr) to afford 4 (127 mg, 98%) as a colorless oil.

IR (film): δ = 3084, 2927, 1754, 1164, 1105 cm⁻¹.

1H NMR (CDCl₃, 250 MHz): δ = 7.45 (dd, J = 5.6, 1.5 Hz, 1 H), 6.08 (dd, J = 5.6, 2.0 Hz, 1 H), 5.77 (ddt, J$_{trans}$ = 17.2 Hz, J = 10.2 Hz, J = 6.6 Hz, 1 H), 5.06 (m, 3 H), 2.21 (m, 2 H), 1.82 (m, 1 H), 1.77 (m, 1 H).

1C NMR (CDCl₃, 62.5 MHz): δ = 172.9, 156.1, 136.6, 121.5, 116.1, 82.5, 32.3, 29.1.

MS: m/z (%) = 139 (M⁺ + 1, 1), 138 (M⁺, 2), 110 (5), 84 (100), 55 (74).

Analog. Calcd for C₄H₇O₂: C, 69.55; H, 7.30; found C, 69.38; H, 7.40.

5-But-3-enyl-1,4-methylfuran-2,5(1H)-one (5)

An ethereal solution of diazomethane (ca 3.80 mmol) prepared from Diazald (1.09 g, 5.09 mmol) was slowly distilled over to a stirred solution of 4 (245 mg, 1.8 mmol) in THF (4 ml) at ~5°C. The mixture was kept in the dark, at r. t. for 24 h, monitoring the reaction by TLC (elucent: EtOAc–hexane, 1:1). Evaporation of the solvent gave a white solid identified as 4-(but-3-enyl)-3a,4,6,6a-tetrahydro-3H-furo[3,4-c]pyrazol-6-one (632 mg, ~100%) which was not further purified.

1H NMR (CDCl₃, 400 MHz): δ = 5.75 (ddt, J$_{trans}$ = 17.0 Hz, J = 10.1 Hz, J = 6.6 Hz, 1 H), 5.50 (td, J = 2.5, 2.2 Hz, 1 H), 5.48 (m, 2 H), 4.82 (dd, J$_{trans}$ = 18.6 Hz, J = 2.5 Hz, 1 H), 4.67 (dd, J$_{cis}$ = 18.6 Hz, J = 8.2 Hz, J = 1.9 Hz, 1 H), 3.92 (m, 1 H), 2.62 (m, 1 H), 2.16 (m, 2 H), 1.78 (m, 1 H), 1.71 (m, 1 H).

1C NMR (CDCl₃, 125 MHz): δ = 168.0, 136.2, 116.3, 94.3, 85.2, 85.1, 37.9, 35.6, 29.1.

This solid was dissolved in freshly distilled 1,4-dioxane (25 ml) and heated at reflux for 48 h, following the reaction progress by TLC (elucent: EtOAc–hexane, 1:1). Evaporation of the solvent under vacuum gave a crude product which was purified by flash chromatography (elucent: EtOAc–hexane, 1:2) affording 5 (185 mg, 69%) as a colorless oil.

IR (film): δ = 3079, 2984, 2924, 1751, 1643, 1439, 1296, 1170 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 5.78 (m, 2 H), 5.03 (m, 2 H), 4.82 (d, J = 7.9 Hz, 1 H), 2.19 (m, 2 H), 2.03 (s, 3 H), 1.97 (m, 1 H), 1.56 (m, 1 H).

1C NMR (CDCl₃, 125 MHz): δ = 173.1, 168.4, 136.7, 117.0, 116.1, 83.8, 31.4, 28.7, 13.8.

HRMS: m/z calcd for C₉H₈O₂ (M⁺) 152.0837, found 152.0842.

MS: m/z (%) = 153 (M⁺ + 1, 1), 152 (M⁺, 2), 110 (12), 98 (100), 69 (40), 41 (79).

5-But-3-enyl-1,3-methylfuran-2,5(1H)-one (6)

To a stirred solution of diisopropylamine (740 µL, 5.5 mmol) in THF (7 mL) under N₂ at 0°C a 1.6 M solution of BuLi in hexane (3.3 mL, 5.3 mmol) and the mixture was stirred at 0°C for 30 min. Then, a solution of phenylselenoacetic acid (516 mg, 2.4 mmol) in THF (10 mL) was added dropwise. A white precipitate was immediately formed. Next, a solution of epoxide 3 (225 µL, 2.0 mmol) in THF (10 mL) was added drop-wise, the cooling bath was removed and the reaction mixture was stirred at r. t. for 5 h. The mixture was acidified with glacial AcOH and the resulting solution was heated at reflux overnight. After neutralization with sat. aq NaHCO₃, the mixture was extracted with Et₂O (3 × 25 mL). The organic extracts were dried (Na₂SO₄) and concentrated to give an oily residue (662 mg) which purified by flash chromatography (elucent: EtOAc–hexane, 1:1) afforded a mixture of cis- and trans-5-(but-3-enyl)-3-phenylseleno-2-oxolanone (662 mg, 97%) as a pale yellow oil.

IR (film): v = 3069, 2980, 2931, 1774, 1474, 1442, 1353, 1183, 1021 cm⁻¹.

1H NMR (CDCl₃, 250 MHz): δ = 7.55 (m, 2 H), 7.25 (m, 3 H), 5.65 (m, 1 H), 4.92 (m, 2 H), 4.32 and 4.23 (m, 1 H), 3.94 (t, J = 9.5 Hz) and 3.86 (dd, J = 6.5, 4.0 Hz) (total 1 H), 2.64 (dd, J = 13.5, 9.5, 6.4 Hz) and 2.30–1.4 (complex absorption) (total 6 H).

1C NMR (CDCl₃, 62.5 MHz): δ = 175.6, 136.8, 136.7, 135.8, 135.7, 135.6, 135.4, 129.4, 129.3, 129.1, 128.8, 115.7, 115.6, 78.7, 78.4, 77.5, 77.0, 76.5, 37.4, 37.0, 36.7, 36.5, 35.8, 34.6, 34.3, 29.3, 29.2.

Anal. Calcd for C₉H₇SeO₂C: C, 56.96; H, 5.46; found C, 56.91; H, 5.56.

To a stirred, cold solution of 5-(but-3-enyl)-3-phenylseleno-2-oxolanone (276 mg, 0.93 mmol) and AcOH (2 drops) in THF (3 mL) was added drop-wise 30% H₂O₂ (0.80 mL, 7.0 mmol), keeping the temperature below 0°C. The mixture was stirred at 0°C for 45 min, then neutralized with sat. aq NaHCO₃ and extracted with Et₂O (3 × 10 mL). The organic extracts were dried (Na₂SO₄) and the solvent evaporated under vacuum. The oily residue was distilled on a Kugelrohr (70–75°C, oven temp./0.06 Torr) to afford 4 (127 mg, 98%) as a colorless oil.

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night. After neutralization with sat. aq NaHCO₃, the mixture was extracted with Et₂O (3 × 200 mL). The organic extracts were dried (Na₂SO₄) and concentrated to give an oily residue which purified by flash chromatography (eluent: EtOAc–hexane, 1:3) afforded a mixture of the two diastereoisomers of 5-(but-3-enyl)-3-phenylseleno-3-methyl-2-oxazolone (3.61 g, 80%)

IR (film): ν = 2962, 2932, 2865, 1770, 1455, 1352, 1231, 1128, 1086 cm⁻¹.

IR (film): ν = 1801 (C=O), 1743 (C=O), 1734 (C=O), 1631 (C=O), 1516 (C=O), 1467 (C=O), 1368 (C=O), 1295 (C=O), 1254 (C=O), 1190 (C=O), 1086 (C=O), 984 (C=O), 864 (C=O), 776 (C=O), 676 (C=O), 588 (C=O), 498 (C=O), 406 (C=O).
Irradiation of 5-But-3-enylfuran-2(5H)-one (4) at Low Temperature; General Procedure
A solution of 4 (89 mg, 0.65 mmol) in acetone (80 mL) at −15 °C was irradiated for 6 h. MeOH was used for refrigeration of the reaction mixture at −15 °C. The reaction progress was monitored by GC. After total conversion of 4, the ratio 7a and 7b was 7:1. The solvent was evaporated and the oily residue was purified by flash chromatography (eluent: CH₂Cl₂–hexane, 1:1) affording a 8:1 mixture of 7a and 7b (45 mg, 51%). Repeated flash chromatography allowed the isolation of a fraction (18 mg) containing a 14:1 mixture (1H NMR analysis) of 7a and 7b.

Irradiation of 5-But-3-enyl-4-methylfuran-2(5H)-one (5) at Low Temperature
Irradiation of 5 (80 mg, 0.53 mmol) at −15 °C following the general procedure showed total conversion of the substrate after 8 h, giving a 8:1 mixture (GC) of 8a and 8b. Purification by flash chromatography (eluent: CH₂Cl₂–hexane, 1:1) afforded a 10:1 mixture of 8a and 8b (46 mg, 58%). A second flash chromatography allowed isolation of 8a (14 mg) of more than 98% purity (1H NMR analysis).

Irradiation of 5-But-3-enyl-3-methylfuran-2(5H)-one (6) at Low Temperature
Irradiation of 6 (74 mg, 0.49 mmol) at −15 °C following the general procedure showed total conversion of the substrate after 5 h, giving a 1:1:1 mixture (GC) of 9a and 9b. Purification by flash chromatography (eluent: CH₂Cl₂–hexane, 1:1) afforded a 1:5:1 mixture of 9a and 9b (41 mg, 55%).

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