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Regioselective 1,6-conjugate addition of organocuprate reagents to γ-alkyldienebutenolides

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1,4- and 1,6-conjugate addition reactions of carbon nucleophiles to electron-deficient alkenes represent a powerful tool for the formation of tertiary or quaternary carbon stereocenters [1]. Due to the poor propagation of the electronic effect through the π-conjugated system (lower reactivity of the δ-position as compared to the β-position), the regioselectivity of the 1,6-conjugate addition reactions is a real challenge to overcome. In addition, γ-alkyldienebutenolides 1 are an important class of naturally occurring γ-lactones endowing with diverse biological properties including herbicidal, antimicrobial, antitumor, antidiabetic and much more [2]. Possessing an α,β,γ,δ unsaturated moiety, as well as a cyclic enol acetate, those γ-lactones are interesting building blocks useful in various synthetic applications [3] and more specifically for the study of the regioselectivity of the 1,6-conjugate addition reactions of organocupper reagents. To the best of our knowledge, only one example was reported by J. Font and coll. [4]. Unfortunately, the regioselective addition of dimethyl- and dibutylcuprates onto protoanemonine, the simplest γ-alkyldienebutenolide 1 (R¹ = R² = R³ = H), proceeded with moderate yields, 27 and 17% respectively. Herein, we wish to report our study on the behavior of the δ-substituted and δ-non-substituted exo-cyclic double bond of γ-alkyldienebutenolides 1 with dialkylcuprates. (Scheme 1).

Our initial plan was to use γ-alkyldienebutenolide 1a (R¹ = H, R² = Me, R³ = Bu) as a model substrate. 1a, as well as the requisite γ-lactones 1, were prepared according to our reported procedure [5]. The reaction was initially performed with 1.5 equivalent of Me₂Cu-Li at 0 °C followed by a saturated aqueous NH₄Cl hydrolysis (Table 1, entry 1). In these conditions, we were delighted to observe that the reaction proceeded in a complete regioselective way. The 1,6-conjugate adduct 2a was obtained in good yield (87%) after the selective α-protonation of the corresponding lithium enolate intermediate.

Quenching the reaction with a buffer solution (NH₄Cl/NH₄OH) at 0 °C or at −78 °C (Table 1, entries 2–3) didn’t improve the isolated yield of 2a.

In addition, no better results (Table 1, entries 4–5) were observed when the reaction was carried out neither with organocopper reagent MeCu-Li nor with higher-order cyanocuprate reagent Me₂Cu-LiCN.

Under the optimal reaction conditions, the scope of 1,6-conjugate addition was then assessed through the variation of the dialkycuprate reagents (Me₂Cu-Li-L, Et₂CuMgMgl and Bu₂Cu-Li-L) and the nature of the substituents R¹ (Me, H), R² (Me, H) and R³ (Bu, H, Ph, CH₂OTBS and CH₂OME) onto the γ-alkyldienebutenolide 1 (Table 2). The methodology was found to be

![Scheme 1. Regioselective 1,6-conjugate addition of organocuprate reagents to γ-alkyldienebutenolides 1.](image-url)
general with an excellent control of the regioselectivity of the conjugate addition affording the desired 1,6-adducts. When $R^2 = \text{Me}$ and $R^3 = \text{Me}$ or $\text{Bu}$ or $\text{CH}_2\text{OTBS}$ (Table 2, entries 1–6), the deconjugated $\gamma$-lactones $2a$ were isolated in acceptable to good yields whatever the nature of the dialkylcuprates. The moderate yield (Table 2, entry 6) of the isolated $2b$-Et could be explained by its degradation during the purification step. Indeed, unidentified compounds, which were non-present in the crude of the reaction, were isolated after the purification step. Interestingly, when $R^3 = \text{CH}_2\text{OTBS}$ is replaced by $R^3 = \text{CH}_2\text{OME}$ (entry 7), the regioselective 1,6-conjugate addition still occurred but with the formation of the conjugated $\gamma$-lactone $3c$-Me (60%), as a 2/1 mixture of two diastereomers, after the selective $\gamma$-protonation of the corresponding lithium enolate intermediate.

The regioselectivity was then assessed by using non-$\beta$-substituted $\gamma$-alkylidenebutenolides $1d$-$1f$ (Table 2, entries 8–10). When $1d$ and $1e$ were subjected to 1.5 eq. of Me$_2$CuLi, we were delighted to observe a total regioselective 1,6-conjugate addition in satisfactory yields. This selectivity was also observed starting from the all conjugated $\gamma$-alkylidenebutenolide $1f$ bearing a phenyl group ($R^2 = \text{H}$, $R^3 = \text{Ph}$) at the $\gamma$-position and promoting the 1,4-addition. Pleasantly, only the 1,6-adduct $2f$-Me was formed.

Table 1
Optimization of reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Me$_2$CuM LiX</th>
<th>hydrolysis</th>
<th>2a/3a/4a yield</th>
<th>Yield 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me$_2$CuLi LiI</td>
<td>NH$_4$Cl, 0 °C</td>
<td>1/0/0</td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td>Me$_2$CuLi LiI</td>
<td>NH$_4$Cl/NH$_4$OH (9/1)</td>
<td>0 °C</td>
<td>66%</td>
</tr>
<tr>
<td>3</td>
<td>Me$_2$CuLi LiI</td>
<td>NH$_4$Cl/NH$_4$OH (9/1) – 78 °C</td>
<td>1/0/0</td>
<td>86%</td>
</tr>
<tr>
<td>4</td>
<td>MeCu LiI</td>
<td>NH$_4$Cl, 0 °C</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Me$_2$CuLi LiCN</td>
<td>NH$_4$Cl, 0 °C</td>
<td>1/0/0</td>
<td>52%</td>
</tr>
</tbody>
</table>

*a Ratio calculated from crude $^1$H NMR.
*b 2 equiv. of TMSCl were used as additive.

Table 2
Scope and Limit of the regioselective 1,6-conjugate addition of organocuprate reagents to $\gamma$-alkylidenebutenolides 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R$^1$CuM MX</th>
<th>2/3/4$^*$</th>
<th>Major Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Me$_2$CuLi LiI</td>
<td>1/0/0</td>
<td>2a-Me</td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Bu$_2$CuLi LiI</td>
<td>1/0/0</td>
<td>2a-Bu</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>Et$_2$CuMg MgI</td>
<td>1/0/0</td>
<td>2a-Et</td>
<td>66%</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>Me$_2$CuLi LiI</td>
<td>1/0/0</td>
<td>2b-Me</td>
<td>62%</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>Bu$_2$CuLi LiI</td>
<td>1/0/0</td>
<td>2b-Bu</td>
<td>47%</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>Et$_2$CuMg MgI</td>
<td>1/0/0</td>
<td>2b-Et</td>
<td>39%</td>
</tr>
<tr>
<td>7</td>
<td>1c</td>
<td>Me$_2$CuLi LiI</td>
<td>0/1/0</td>
<td>3c-Me</td>
<td>60% d.r. = 2:1</td>
</tr>
<tr>
<td>8</td>
<td>1d (Z/E:9/1)</td>
<td>Me$_2$CuLi LiI</td>
<td>1/0/0</td>
<td>2d-Me</td>
<td>78%</td>
</tr>
<tr>
<td>9</td>
<td>1e (Z/E:86/14)</td>
<td>Me$_2$CuLi LiI</td>
<td>1/0/0</td>
<td>2e-Me</td>
<td>46%</td>
</tr>
<tr>
<td>10</td>
<td>1f</td>
<td>Me$_2$CuLi LiI</td>
<td>1/0/0</td>
<td>2f-Me</td>
<td>54%</td>
</tr>
<tr>
<td>11</td>
<td>1g</td>
<td>Me$_2$CuLi LiI</td>
<td>0/1/0</td>
<td>3g-Me</td>
<td>52%</td>
</tr>
<tr>
<td>12</td>
<td>1g</td>
<td>Bu$_2$CuLi LiI</td>
<td>0/1/0</td>
<td>3g-Bu</td>
<td>41%</td>
</tr>
<tr>
<td>13</td>
<td>1a</td>
<td>Me$_2$CuLi LiI$^b$</td>
<td>7/93/0</td>
<td>3a-Me</td>
<td>56% d.r. = 7:3</td>
</tr>
</tbody>
</table>

*a Ratio calculated from crude $^1$H NMR.
*b 2 equiv. of TMSCl were used as additive.
(entry 10) without observing the presence of the other regioisomer arising from the 1,4-conjugate addition. In addition, starting from non-δ-substituted γ-alkylidenebutenolide 1h (Table 2, entries 11–12), the regioselective 1,6-conjugate addition of Me₂CuLi·Li and Bu₂CuLi·Li occurred to give after purification, the conjugated γ-lactones 3g-Me and 3g-Bu in 52 and 41% yield respectively.

Finally, the 1,6-conjugate addition of Me₂CuLi·Li to δ-substituted γ-alkylidenebutenolide 1a was then performed by using 2 eq. of chlorotrimethylsilane as additive [6]. Unfortunately, these conditions did not increase the yield of the reaction but, interestingly, allow us to mainly obtain, in moderate yield, the conjugated γ-lactone 3a-Me, as a 7:3 mixture of 2 diastereomers, instead the deconjugated γ-lactones 2 (Table 2, entries 13). With these conditions in hand, we have a tunable 1,6-conjugate addition towards either deconjugated γ-lactones 2 or conjugated γ-lactones 3 starting from β-substituted γ-alkylidenebutenolides.

In conclusion, the conjugate addition of dialkylcuprate onto δ-substituted γ-alkylidenebutenolides is described. This addition was found to be highly regioselective to afford the corresponding 1,6-conjugate adduct.

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