Synthesis of Ene-ynamide Derivatives Starting from Baylis-Hillman Adducts: Isomerization with the Aid of \( \pi \)-Cation Interaction

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Recently, we have developed a facile synthetic method of 9-phenyl-7\( H \)-benzocycloheptene derivatives from the alkylnyl moiety-containing Baylis-Hillman adducts, which involved intramolecular Friedel-Crafts alkenylation reaction of triple bond-tethered methyl cinnamates.\(^1\) We also reported the synthesis of iodoenol lactones from the same substrates via the typical iodolactonization protocol.\(^2\) During the investigation we envisaged that we could prepare the corresponding lactam derivatives from the amides of the Baylis-Hillman adducts by using similar strategy as shown in Scheme 1.\(^3,4\) However, during the investigation for the synthesis of lactam derivatives from 3, we found the formation of isomerized conjugated ene-ynamide derivatives 4 unexpectedly and wish to report herein the results (Scheme 1).

Conjugated\(^5-7\) or non-conjugated\(^8\) ene-ynamides are frequently used as synthetic intermediates, and as a key backbone of \( \beta \)-turn mimetics, tweezers-type host molecules, and a basic unit of molecular nanostructures.\(^7\)

The triple bond-containing amide derivatives 3 were prepared from the corresponding ester 2.\(^1\) Hydrolysis of 2 in aq THF with LiOH and the following condensation with appropriate amines by using 1,1'-carbonyldiimidazole afforded 3 in moderate yields (61-82%) and the results are summarized in Table 1. Initially, we tried many reaction conditions including \( I_2/NaHCO_3 \), \( I_2/K_2CO_3 \), \( I_2/LiHMDS \) (lithium bis(trimethylsilyl)amide) in order to synthesize the original target compounds, lactam derivatives. But, all the efforts resulted in failure for the synthesis of lactam derivatives. Thus, as a next choice, we examined the possibility for the lactamization in the presence of a strong base such as NaH, \( \eta \)-BuLi, or LiHMDS without the aid of electrophile like iodine. However, we observed the unusual formation of conjugated ene-ynamide 4a in low yield from 3a instead of the desired lactam derivative when we used LiHMDS, unexpectedly.

Intrigued by the results we examined the isomerization conditions deeply and finally we could increase the yield of 4a up to 60%, under the influence of LiHMDS (1.1 equiv, THF). The structure of 4a was confirmed by IR, \(^1\)H, \(^13\)C, and mass spectroscopy. The synthesis of ene-ynamide is very important as mentioned above,\(^5,7\) thus we examined the isomerization reactions of 3b-e and the results are summarized in Scheme 1 and in Table 1. As shown, the isomerization for 3a-e occurred effectively with the aid of LiHMDS (1.1 equiv.) in THF at room temperature. Use of less amounts of LiHMDS resulted in dramatic decrease in yields. The isomerization of 3d and 3e did not occur, however, under the same conditions (condition A). After devoting much efforts we finally found that the combination
of Sc(OTf)₃ (0.1 equiv) and LiHMDS (0.3 equiv) could convert 3d and 3e into 4d and 4e, respectively, in reasonable yields.

The trials for the isomerization with the ester derivatives 2a and 2b failed completely under the similar reaction conditions. Remaining starting materials and small amounts of intractable mixtures were observed in the reaction mixtures. From the results we supposed that the amide proton of 3 might act in any way during the isomerization process. Although we could not explain the reaction mechanism exactly at this stage, we could propose the isomerization process tentatively as shown in Scheme 2.

Initially, relatively acidic amide proton of 3 might act in any way during the isomerization process. In the lithiated amide anion, there might be π-cation interaction between triple bond and lithium ion (vide infra) to form the six-membered stabilized intermediate (I). Residual LiHMDS acts as an external base to deprotonate the proton at the allylic position (the acidity of the allylic proton might be increased also by the π-cation interaction) and caused the rearrangement as shown in Scheme 2 for 3a-c. For the phenyl-substituted substrates, 3d and 3e, Sc(OTf)₃ can replace the role of Li cation during the isomerization process although we could not explain exactly at this stage. The necessity of the acidic amide proton for the successful isomerization could be confirmed once again by the failure of 3f, a tertiary amide, under the same conditions (Scheme 3).

The stereochemistry of the double bond of 4a-e was thought to be as (Z) based on the NOE experiments with 4e (R = Ph, R’ = cyclohexyl, shown in Scheme 2). Irradiation of the vinyl proton of 4e showed NOE increments of 2.3% and 0.6% of the benzylic protons and aromatic protons, respectively. The stereochemistry can also be explained well by using the proposed reaction mechanism in Scheme 2.

In addition, when we compared the relative energies of 3a and 4a by MM2 calculation, we found that 4a was more stable than 3a in about 2.5 kcal/mol presumably due to π-triple bond-H (amide proton) interaction. In the energy-minimized conformations of 3a and 4a, we could observe that the distance between the amide proton and the triple bond of 4a is closer than that of 3a. We are currently investigating the detailed stabilization effect of π-cation and π-proton with B3LYP and the results will be published in due course.

In summary, we prepared some ene-ynamides starting from the Baylis-Hillman adducts. During the investigations, we found that π-cation interactions could increase the acidity of the nearby protons of triple bond of non-conjugated ene-

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### Table 1. Synthesis of conjugated ene-ynamides 4a-e

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions a</th>
<th>Yield (%)</th>
<th>Conditions b</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₂NH₂, 10 h</td>
<td>3a (69)</td>
<td>A, 7 h</td>
<td>4a (60)</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅NH₂, 12 h</td>
<td>3b (62)</td>
<td>A, 5 h</td>
<td>4b (84)</td>
</tr>
<tr>
<td>3</td>
<td>PhNH₂, 12 h</td>
<td>3c (82)</td>
<td>A, 11 h</td>
<td>4c (70)</td>
</tr>
<tr>
<td>4</td>
<td>PhCH₂NH₂, 6 h</td>
<td>3d (61)</td>
<td>B, 30 min</td>
<td>4d (55)</td>
</tr>
<tr>
<td>5</td>
<td>C₆H₅NH₂, 10 h</td>
<td>3e (65)</td>
<td>B, 30 min</td>
<td>4e (62)</td>
</tr>
</tbody>
</table>

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*a (i) LiOH (1.5 equiv), aq THF, rt, 20 h; (ii) Im₂CO (1.1 equiv), amine (1.5 equiv), CH₂Cl₂, rt, 8-12 h; b Conditions A: LiHMDS (1.1 equiv), THF, 0°C-rt; Conditions B: LiHMDS (0.3 equiv), Sc(OTf)₃ (0.1 equiv), THF, 0°C-rt*
ynamide and could make come true the isomerization into a more stable conjugated ene-ynamide form.

**Experimental Section**

**Typical procedure for the amide derivatives 3:** The corresponding methyl cinnamates 2 were made from the acetates of Baylis-Hillman adduct 1 as previously reported. 1

Hydrolysis of 2 to the corresponding cinnamic acid derivatives was easily conducted with LiOH in aqueous THF (rt, 20 h). After the hydrolysis, simple aqueous workup, and removal of solvent gave almost pure cinnamic acids and we used them without further purification step. A stirred solution of the cinnamic acid (prepared from 2a) (108 mg, 0.54 mmol) and 1,1'-carbonyldiimidazole (97 mg, 0.60 mmol) in dichloromethane (3 mL) was kept for 1 h at room temperature. To the reaction mixture benzylamine (87 mg, 0.81 mmol) was added and stirred at room temperature for 9 h. After the usual workup and column chromatographic purification process (hexanes/EtOAc, 95 : 5) we obtained 3a as clear oil, 108 mg (69%). The spectroscopic data of prepared compounds 3a-e are as follows.

**Compound 3a:** 69%; oil; IR (neat) 3321, 1651, 1620, 1531 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.76 (t, $J$ = 2.7 Hz, 3H), 3.31 (q, $J$ = 2.7 Hz, 2H), 4.61 (d, $J$ = 5.7 Hz, 2H), 6.72 (br s, 1H), 7.26-7.43 (m, 10H), 7.55 (s, 1H).

**Compound 3b:** 62%; white solid, mp 124-125 °C; IR (neat) 3325, 2931, 1616, 1535 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.76 (t, $J$ = 2.7 Hz, 3H), 3.31 (q, $J$ = 2.7 Hz, 2H), 4.61 (d, $J$ = 5.7 Hz, 2H), 6.72 (br s, 1H), 7.26-7.43 (m, 10H), 7.55 (s, 1H).

**Compound 3c:** 60%; oil; IR (neat) 3483, 1647, 1535 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.91 (t, $J$ = 2.7 Hz, 3H), 3.40 (q, $J$ = 2.7 Hz, 2H), 7.11-7.17 (m, 5H), 7.25-7.64 (m, 10H), 8.29 (br s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 3.78, 18.48, 24.76, 25.87, 33.10, 48.47, 76.23, 78.55, 128.36, 128.69, 129.38, 131.68, 135.70, 135.80, 167.27.

**Compound 3d:** 61%; white solid, mp 95-97 °C; IR (neat) 3440, 1647, 1535 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.61 (s, 2H), 4.63 (d, $J$ = 5.7 Hz, 2H), 6.68 (t, $J$ = 5.7 Hz, 1H), 7.18-7.45 (m, 15H), 7.60 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 18.96, 44.19, 82.82, 86.15, 122.85, 127.51, 127.80, 128.20, 128.25, 128.45, 128.61, 128.77, 129.22, 130.73, 131.67, 135.28, 136.33, 138.11, 167.78.

**Compound 3e:** 65%; white solid, mp 173-175 °C; IR (neat) 3302, 2931, 2241, 1620, 1535 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.13-1.76 (m, 8H), 1.95-2.02 (m, 2H), 3.57 (s, 2H), 3.90-4.02 (m, 1H), 6.30 (d, $J$ = 8.1 Hz, 1H), 7.28-7.48 (m, 10H), 7.53 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 38.26, 86.57, 123.23, 128.43, 128.52, 128.79, 129.42, 131.34, 131.83, 135.70, 136.02, 167.18.

**Compound 3f:** 60%; oil; IR (neat) 1628, 1427, 1115 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.66 (d, $J$ = 0.9 Hz, 2H), 3.69 (t, $J$ = 4.2 Hz, 4H), 3.78 (t, $J$ = 4.2 Hz, 4H), 6.59 (s, 1H), 7.25-7.45 (m, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 18.26, 25.87, 33.10, 48.47, 76.23, 78.55, 128.36, 128.69, 129.38, 131.68, 135.70, 135.80, 167.27.
Compound 4a: 60%; white solid, mp 78-80 °C; IR (neat) 3386, 2924, 2217, 1689, 1651, 1527 cm⁻¹; ¹H NMR (CDCl₃) δ 1.74 (d, J = 2.7 Hz, 3H), 3.74 (s, 2H), 4.51 (d, J = 5.4 Hz, 2H), 5.56-5.69 (m, 1H), 7.17-7.35 (m, 1H); ¹³C NMR (CDCl₃) δ 48.53, 39.77, 44.11, 76.86, 96.37, 112.17, 126.68, 127.65, 128.11, 128.75, 128.89, 129.45, 138.19, 138.82, 145.85, 166.16; Mass (70 eV) m/z (rel. intensity) 77 (18), 91 (100), 115 (25), 153 (20), 198 (18), 289 (M⁺, 30).

Compound 4b: 64%; white solid, mp 105-107 °C; IR (neat) 3290, 2935, 2222, 1631, 1543 cm⁻¹; ¹H NMR (CDCl₃) δ 10.10-1.71 (m, 8H), 1.85-1.92 (m, 2H), 2.00 (d, J = 2.7 Hz, 3H), 3.69 (s, 2H), 3.81-3.94 (m, 1H), 5.59-5.63 (m, 1H), 6.91 (br, s, 1H), 7.16-7.30 (m, 5H); ¹³C NMR (CDCl₃) δ 4.75, 24.96, 25.86, 33.03, 39.73, 48.11, 77.01, 95.50, 111.35, 126.59, 128.69, 129.43, 138.94, 146.78, 165.43.

Compound 4c: 70%; white solid, mp 119-121 °C; IR (neat) 3221, 1631, 1597 cm⁻¹; ¹H NMR (CDCl₃) δ 2.08 (d, J = 2.4 Hz, 3H), 4.01 (s, 2H), 6.70 (q, J = 2.4 Hz, 1H), 7.02-7.08 (m, 1H), 7.22-7.29 (m, 10H); ¹³C NMR (CDCl₃) δ 31.24, 25.72, 77.43, 97.80, 119.12, 120.08, 124.61, 127.43, 128.63, 129.15, 129.40, 137.87, 138.19, 143.50, 165.27.

**Typical procedure for the isomerization of 3d to 4d:** To a stirred solution of 3d (105 mg, 0.3 mmol) in dry THF (1 mL) was added Sc(OF₅)(15 mg, 0.03 mmol) and LiHMDS (0.1 mL, 0.1 mmol, 1.0 mol solution in THF) successively at 0 °C under nitrogen atmosphere and the reaction mixture was stirred further 30 min at room temperature. After the usual workup and column chromatographic purification process (hexanes/EtOAc, 95: 5) we obtained 4d as clear oil, 58 mg (55%). The spectroscopic data of prepared compounds 4d and 4e are as follows.

**Compound 4d:** 55%; white solid, mp 100-102 °C; IR (neat) 2195, 1693, 1655 cm⁻¹; ¹H NMR (CDCl₃) δ 3.82 (d, J = 1.5 Hz, 2H), 4.55 (d, J = 5.4 Hz, 2H), 5.93 (t, J = 1.5 Hz, 1H), 6.99-7.03 (m, 2H), 7.18-7.34 (m, 14H); ¹³C NMR (CDCl₃) δ 40.10, 44.26, 85.76, 98.70, 111.44, 126.84, 127.72, 128.30, 128.60, 128.86, 129.97, 129.21, 129.58, 131.60, 138.05, 138.56, 146.90, 166.13.

**Compound 4e:** 62%; white solid, mp 127-130 °C; ¹H NMR (CDCl₃) δ 1.03-1.70 (m, 8H), 1.89-1.95 (m, 2H), 3.76 (d, J = 1.5 Hz, 2H), 3.82-3.94 (m, 1H), 5.86 (t, J = 1.5 Hz, 1H), 6.74 (d, J = 6.6 Hz, 1H), 7.20-7.42 (m, 10H); ¹³C NMR (CDCl₃) δ 24.89, 25.78, 33.23, 48.58, 85.90, 97.85, 110.55, 122.56, 126.77, 127.88, 128.76, 128.80, 129.21, 129.53, 131.55, 138.61, 147.90, 165.47.

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**References and Notes**