Synthesis of Ene-ynamide Derivatives Starting from Baylis-Hillman Adducts: Isomerization with the Aid of π-Cation Interaction

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Received June 3, 2005

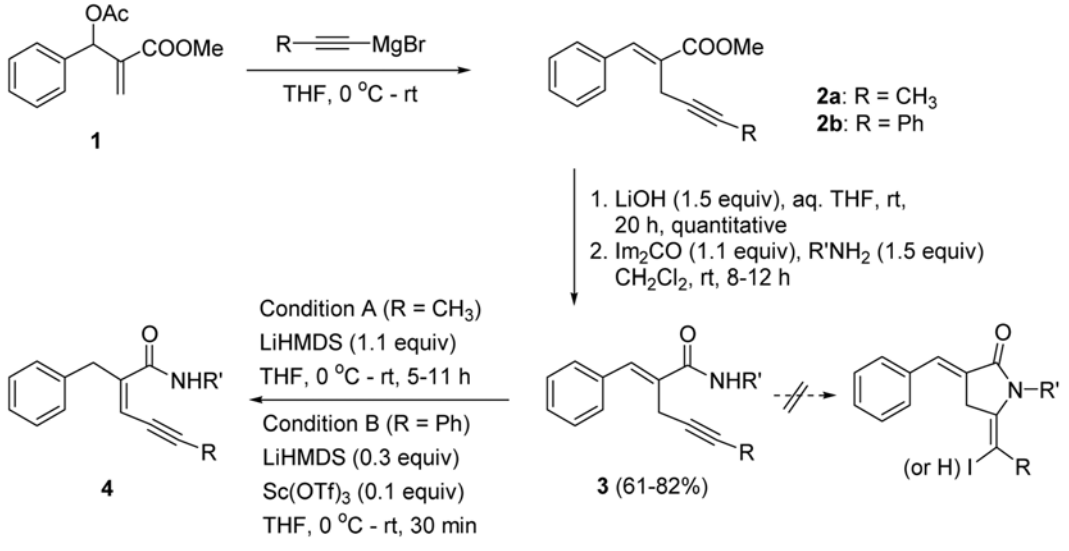
Key Words : Ene-ynamides, Baylis-Hillman adducts, π-Cation interaction

Recently, we have developed a facile synthetic method of 9-phenyl-7*H*-benzocycloheptene derivatives from the alkynyl 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 acetates 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 β-turn mimetics, tweezers-type host molecules, and a basic unit of molecular nanostructures.[7]

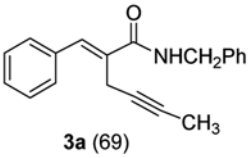
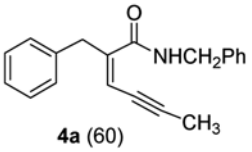
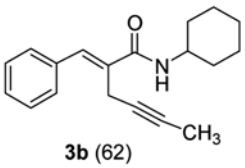
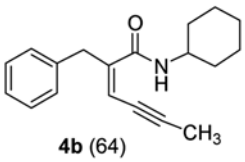
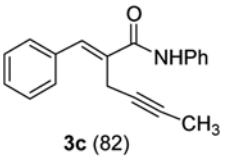
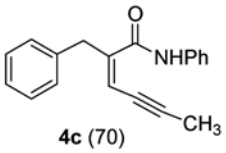
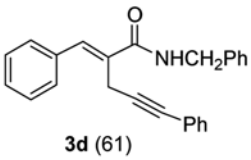
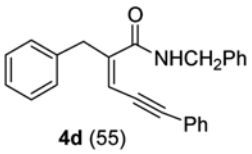
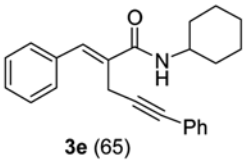
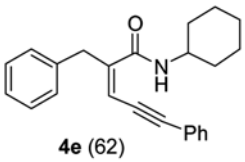
The triple bond-containing amide derivatives **3** were prepared from the corresponding ester **2**.[1] Hydrolysis of **2** in aq THF with LiOH and the following condensation with appropriate amines by using 1,1'-carbonyldiimidazole afforded **3** in moderate yields (61-82%) and the results are summarized 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, *n*-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 conformed 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-c** 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



Scheme 1

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

Entry	**2**	conditions[a]	**3** (%)	conditions[b]	**4** (%)
1	**2a**	$PhCH_2NH_2$ 10 h	 **3a** (69)	A 7 h	 **4a** (60)
2	**2a**	$C_6H_{11}NH_2$ 10 h	 **3b** (62)	A 5 h	 **4b** (64)
3	**2a**	$PhNH_2$ 12 h	 **3c** (82)	A 11 h	 **4c** (70)
4	**2b**	$PhCH_2NH_2$ 8 h	 **3d** (61)	B 30 min	 **4d** (55)
5	**2b**	$C_6H_{11}NH_2$ 10 h	 **3e** (65)	B 30 min	 **4e** (62)

[a](i) LiOH (1.5 equiv), aq THF, rt, 20 h; (ii) Im_2CO (1.1 equiv), amine (1.5 equiv), CH_2Cl_2, 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

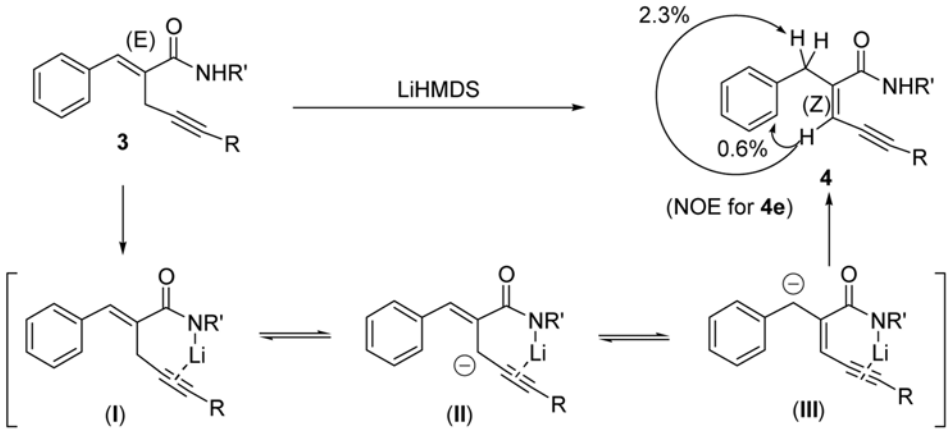
of $Sc(OTf)_3$ (0.1 equiv) and LiHMDS (0.3 equiv) could convert **3d** and **3e** into **4d** and **4e**, respectively, in reasonable yields.[9]

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** was deprotonated with LiHMDS. In the lithiated amide anion, there might be π-cation interaction[10] between triple bond and lithium ion (vide infra) to form the six-membered stabilized intermediate (**I**).[4,10e,11] 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).

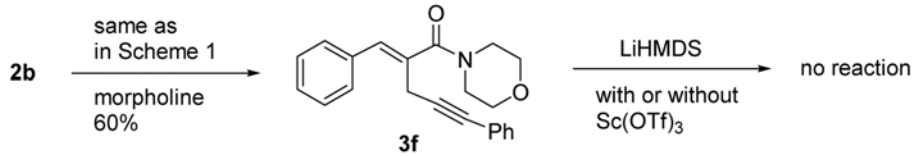
The stereochemistry of the double bond of **4a-e** was thought to be as (*Z*) based on the NOE experiments with **4e** (R = Ph, R' = cyclohexyl, shown in Scheme 2). Irradiation of the vinyl proton of **4e** showed NOE increments of 2.3% and 0.6% of the benzylic protons and aromatic protons, respectively. 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.[10] 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-



Scheme 2



Scheme 3

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}; ^1H NMR ($CDCl_3$) δ 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) 3275, 2931, 1616, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22-1.77 (m, 8H), 1.85 (t, J = 2.4 Hz, 3H), 1.95-2.01 (m, 2H), 3.27 (q, J = 2.4 Hz, 3H), 3.93-3.97 (m, 1H), 6.37 (d, J = 6.9 Hz, 1H), 7.29-7.42 (m, 5H), 7.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 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 **3c**: 82%; white solid, mp 130-132 °C; IR (neat) 3483, 1647, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (t, J = 2.7 Hz, 3H), 3.40 (q, J = 2.7 Hz, 2H), 7.11-7.17 (m, 1H), 7.25-7.64 (m, 10H), 8.29 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 3.91, 18.55, 76.01, 79.27, 120.31, 124.60, 128.75, 128.83, 129.29, 129.47, 131.67, 135.44, 137.05, 138.36, 166.38. Compound **3d**: 61%; white solid, mp 95-97 °C; IR (neat) 3440, 1647, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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}; ^1H NMR ($CDCl_3$) δ 1.13-1.76 (m, 8H), 1.96-2.02 (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 ($CDCl_3$) δ 19.22, 24.84, 25.81, 33.19, 48.67, 82.86, 86.57, 123.23, 128.43, 128.52, 128.56, 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}; ^1H NMR ($CDCl_3$) δ 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, 10H); ^{13}C NMR ($CDCl_3$) δ 20.66, 67.08 (br), 82.26, 85.55, 129.14, 128.12, 128.15, 128.36, 128.62, 128.87, 130.37, 131.23, 131.52, 134.83, 170.76.

Typical procedure for the isomerization of 3a to 4a: To a stirred solution of **3a** (101 mg, 0.35 mmol) in dry THF (1 mL) was added LiHMDS (0.39 mL, 0.39 mmol, 1.0 mol solution in THF) slowly at 0 °C under nitrogen atmosphere and the reaction mixture was stirred further 7 h at room temperature. After the usual workup and column chromatographic purification process (hexanes/EtOAc, 95 : 5) we obtained **4a** as a white solid, 61 mg (60%). The spectroscopic data of prepared compounds **4a-c** are as follows.

Compound **4a**: 60%; white solid, mp 78-80 °C; IR (neat) 3386, 2924, 2217, 1689, 1651, 1527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (d, J = 2.7 Hz, 3H), 3.74 (s, 2H), 4.51 (d, J = 5.4 Hz, 2H), 5.66-5.69 (m, 1H), 7.17-7.35 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 4.53, 39.77, 44.11, 76.86, 96.37, 112.17, 126.68, 127.65, 128.11, 128.75, 128.88, 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 ($CDCl_3$) δ 1.10-1.71 (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); ^{13}C NMR ($CDCl_3$) δ 4.75, 24.69, 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) 2221, 1651, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) 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), 7.22-7.39 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 1.24, 35.72, 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 $Sc(OTf)_3$ (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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 40.10, 44.26, 85.76, 98.70, 111.44, 126.84, 127.72, 128.30, 128.60, 128.86, 128.97, 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 24.89, 25.78, 33.23, 48.58, 85.90, 97.85, 110.55, 122.56, 126.77, 128.77, 128.76, 128.80, 129.21, 129.53, 131.55, 138.61, 147.90, 165.47.

Acknowledgments. This work was supported by the grant (R-05-2003-000-10042-0) from the Basic Research Program of the Korea Science and Engineering Foundation (Now controlled under the authority of Korea Research Foundation). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

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11. During the evaluation process of this paper one of the reviewers suggested the NMR monitoring experiments. However we could not carry out the experiments due to the presence of many intractable side products in the reaction mixtures. For such NMR experiments of π-complexation, see Nilsson, K.; Ullenius, C.; Krause, N. *J. Am. Chem. Soc.* **1996**, *118*, 4194 and for the alkali metal cation-π interactions including triple bond, see the reference 10(e).