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<thead>
<tr>
<th>項目</th>
<th>内容</th>
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<tr>
<td>タイトル</td>
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<td>author</td>
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Graphical Abstract

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Ti(II)-Mediated domino cyclization of 2-functionalized 1-halo-2,n-enynes (n = 7, 8) to bicyclic compounds

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The reaction of 2-functionalized 1-halo-2,n-enynes with Ti(O-i-Pr) 4/2i-PrMgCl proceeded in a domino fashion to yield bicyclic compounds.
Ti(II)-Mediated domino cyclization of 2-functionalized 1-halo-2,n-enynes (n = 7, 8) to bicyclic compounds

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Abstract—The reaction of 2-functionalized 1-halo-2,n-enynes (n = 7 or 8) with a divalent titanium reagent, Ti(O-i-Pr)2/2-i-PrMgCl, proceeded in a domino fashion to afford bicyclic compounds in good yields. © 2011 Elsevier Science. All rights reserved

We have recently developed a divalent titanium reagent-mediated cyclization of 2,7- and 2,8-enyn-1-ol derivatives. Thus, the reaction of enyn-1-ol derivatives 2 (G = H) with Ti(O-i-Pr)2/2-i-PrMgCl (1) proceeded through β-elimination of the leaving group X from a titanacyclic intermediate 3 (G = H) to give alkenyltitanium compound 4 (Scheme 1). The resulting alkenyltitaniums 4 could act as a nucleophile and reacted with various electrophiles to give 5. With these results in hand, we thought that further intramolecular cyclization of the resulting alkenyltitaniums of the type 4 to bicyclic compounds might occur in a domino fashion when the starting enynes have a functional group (FG), which can react with the alkenyltitanium moiety, as a substituent G at a C-2 position (Scheme 1). Herein reported is the realization of this idea by introducing -CO2R or -CH2Cl as the FG at a C-2 position of 2,7- and 2,8-enyn-1-ol derivatives, which might be expected to produce the corresponding bicyclic products 6 and 7, respectively.

First, we investigated the 1-mediated reaction of 2a, which has a methoxycarbonyl group as the substituent G (Table 1). Thus, enynol derivative 2a was treated with 1.4 equiv of 1 at −40 to −20 °C for 2 h and the mixture was quenched by addition of H2O. However, the expected dienone 6a was not produced but 29% of enone compound 8 was produced with 37% of the recovered 2a (Table 1, entry 1).

Scheme 1. Plan for domino reaction.

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Table 1. Reactions of 5 with 1.

<table>
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<th>entry</th>
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<th>equiv of 1</th>
<th>yield, %</th>
<th>recovered 2</th>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>1.4</td>
<td>29</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>2.3</td>
<td>84</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>1.4</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>2c</td>
<td>1.4</td>
<td>trace</td>
<td>93</td>
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Therefore, we carried out the reaction using 2.3 equiv of 1 and found that the reaction provided 8 [diastereomeric ratio (d.r.) = 95:5] in 84% yield (Table 1, entry 2). Enynes 2 having a more sterically demanding ester group reacted smoothly with 1.4 equiv of 1 but afforded mono-cyclic compounds 9 as a major product (entries 3 and 4).

The results can be explained by assuming that the reaction of 2a with 1 provided dienone 6a via 4’a as expected, however, the resulting 6a further reacted with 1 fast to afford the corresponding oxatitanacyclic compound 10, hydrolysis of which gave 8 (the order of reaction rates: \(k_2\), \(k_3 > k_1\)) (Scheme 2). Introduction of cyclohexyl group into an ester moiety relatively decreased the reaction rate from the corresponding 4’ to 6a \((k_2)\) and, therefore, the reaction provided a mixture of 8 and 9 \((k_1, k_3 > k_1)\). t-Bu group may be so bulky that intramolecular acyl substitution reaction of the corresponding 4’ could not undergo.

Scheme 2. Possible explanation for formation of 8 and 9.

The presence of an intermediate 10 was confirmed by iodolysis of the reaction mixture derived from 2a and 2.3 equiv of 1 (Scheme 3): The reaction mixture was treated with I\(_2\) to give 6a in 62% yield. Thus, Ti(II)-mediated domino cyclization could provide bicyclic compounds 6a and 8 having a cyclopentene and methylene cyclopentene structures, respectively, from the acyclic enyne starting compound.

Scheme 3. Formation of 6a by the reaction of 10 with I\(_2\).

Next, we prepared enyne 2d as a substrate which has a chloromethyl moiety as the substituent G at the C-2 position, expecting that the corresponding titanium compound 4’d could undergo intramolecular allylic substitution giving 7d (Scheme 4). Treatment of 2d with 1.2 equiv of 1, however, resulted in production of mono-cyclic compound 11 after hydrolysis. The results indicate that generated alkenyltitanium 4’d could not undergo allylic substitution. It was found that addition of a catalytic amount of Li\(_2\)Cu(CN)Cl\(_2\) to the reaction mixture of 4’d could effect intramolecular allylic substitution to produce 1,2-annulated fuluvenes 7d in 80% yield.

Scheme 4. Reaction of 2d with 1 and the following Cu-catalyzed cyclization.

Under similar reaction conditions, analogous compounds 2e-2g reacted smoothly with a divalent titanium reagent 1 and then Li\(_2\)Cu(CN)Cl\(_2\) catalyst to afford the corresponding 1,2-annulated fuluvenes 7e-7g, respectively, in good yield (Scheme 5). High 1,2-diastereoselectivity was observed in the reaction of 2g.
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Acknowledgments

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Scheme 6 illustrates preparation of the substrates 2 for the present cyclization reactions. Thus, compounds 2a–c were synthesized by the Baylis-Hillman reaction of acrylic esters with 6-trimethylsilylhex-5-ynal (12) followed by bromination of the resulting alcohols, where the bromination reaction proceeded stereoselectively to yield the corresponding bromoesters as a Z isomer. While, compounds 2d–f were prepared from the known 5-bromomethylene-2,2-dimethyl-[1,3]dioxane (13) by Suzuki-Miyaura coupling reaction and the following cleavage of ketal and chlorination of the resulting diols. Compound 2g was obtained via the lithiation of 13 and the reaction with aldehyde 12.

In summary, we have demonstrated that a divalent titanium reagent could effectively cyclize 2-functionalized 2,7- and 2,8-enyn-1-ol derivatives in a domino fashion to provide bicyclic compounds. The synthetic application of the present method is now underway in our laboratory.

References


5. Compound 8: To a solution of 2a (1.0 mmol) and Ti(O-i-Pr)₄ (2.3 mmol) in ether (10 mL) was added i-PrMgCl (4.6 mmol, 0.97 M in ether) at -40 °C and the mixture was stirred for 2 h at this temperature. After addition of aqueous 1M HCl, usual extractive work-up was followed; ¹H NMR (300 MHz, CDCl₃) δ 2.39-2.70 (m, 3H), 2.18 (dt, J = 12, 6.6 Hz, 1H), 1.83-2.11 (m, 4H), 1.19 (d, J = 7.2 Hz, 3H), 0.18 (s, 9H).

Compound 9c: ¹H NMR (300 MHz, CDCl₃) δ 6.12 (br s, 1H), 5.43 (br s, 1H), 5.20 (q, J = 2.1 Hz, 1H), 3.36-3.43 (m, 1H), 2.33-2.46 (m, 2H), 1.40-1.97 (m, 4H), 1.47 (s, 9H), 0.08 (s, 9H).

Compound 6a: To the reaction mixture derived from 2a (1.0 mmol) and I (2.3 mmol) prepared above was added a solution of I₂ (2.3 mmol) in ether at –20 °C. After addition of aqueous 1M HCl, usual extractive work-up was followed; ¹H NMR (300 MHz, CDCl₃) δ 5.91 (br s, 1H), 5.26 (br s, 1H), 3.27-3.37 (m, 1H), 2.50-2.75 (m, 2H), 1.90-2.25 (m, 2H), 1.08-1.30 (m, 2H), 0.21 (s, 9H).

Compound 7d: To a solution of 2d (1.0 mmol) and Ti(O-i-Pr)₄ (1.2 mmol) in ether (10 mL) was added i-PrMgCl (2.4 mmol, 0.97 M in ether) at –40 °C and the mixture was stirred for 3 h at –40 °C. To the mixture was added Li₂Cu(CN)Cl₂ (0.1 mmol, 1.0 M in THF) and the mixture was gradually warmed to room temperature over 2 h. After addition of water (0.3 mL), NaF (1 g) and Celite (1 g), the mixture was filtered through a pad of Celite. The filtrate was concentrated and purified by column chromatography on silica gel; ¹H NMR (300 MHz, CDCl₃) δ 4.80 and 4.75 (2 br s, each 1H), 3.37-3.52 (m, 2H), 3.16 (d, J = 18.6 Hz, 1H), 2.16-2.25 (m, 2H), 1.90-2.05 (m, 3H), 1.08-1.25 (m, 1H), 0.08 (s, 9H).

Compound 11: ¹H NMR (300 MHz, CDCl₃) δ 5.29 (br s, 2H), 5.05 (s, 1H), 4.04 and 3.99 (2d, each J = 12.6 Hz, each 1H), 3.26 (t, J = 6.3 Hz, 1H), 2.14-2.54 (m, 2H), 1.51-2.03 (m, 4H), 0.08 (s, 9H).

6. Stereochemistries of compounds 8 and 7g were determined by ¹H-¹H cosy and noesy experiments. Explanation of these stereoselectivities must await further study.