Regioselective Intermolecular [2 + 2]-Cycloaddition of α-Iodo-Unsaturated Ketones Promoted by Diisobutylaluminum Hydride

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Supporting Information

ABSTRACT: The development of intermolecular [2 + 2]-cycloaddition of α-iodo-unsaturated ketones in the presence of diisobutylaluminum hydride (Dibal-H) is reported to produce various trispirocyclic derivatives containing a cyclobutane ring. This sequential lactonization/[2 + 2]-cycloaddition proceeds in high regioselectivity under mild conditions.

Cyclobutane fragments were found in biologically important natural products and utilized as useful intermediates for the construction of more complex systems. Therefore, the construction of cyclobutane subunits has continued to receive much attention. Compared with other strategies, the [2 + 2]-cycloaddition reactions stand out as more efficient methods for the preparation of such annulation systems with high atom economy. To date, the [2+2]-cycloaddition of intramolecular or intermolecular alkenes has been extensively investigated photochemically and thermally. Additionally, the [2 + 2]-cycloaddition reactions between alkenes and allenes have also been successfully developed to construct cyclobutanes with excellent efficiency. Despite these advances, the selective [2 + 2]-cycloaddition of allenes for the production of the complex cyclobutanes has been explored limitedly. Thus, the development of concise and efficient [2 + 2]-cycloaddition of allenes, including mild, commercially available reagents, and excellent selectivity, remain of practical significance.

Reportedly, allenes bearing an electron-donating group at the distal end would express stronger nucleophilicity and, consequently, be more likely to perform the [2 + 2]-cycloaddition reaction in a regio- and stereoselective manner. Initially, Zhang developed a tandem cationic Au-catalyzed [2 + 2]-cycloadditions of allenyl esters in situ generated from propargylic esters with high efficiency and regioselectivity (Scheme 1, eq 1). In 2011, Chan described the [2 + 2]-cycloaddition of 1,7-enebenzoates to prepare functionalized 1-tosyl-1,2,3,6-tetrahydropyridine-fused cyclobutanes involving an activated allene intermediate (Scheme 1, eq 2). Although these methods showed incomparable ingenuity and originality for the synthesis of cyclobutanes, the use of expensive Au(1) complexes as catalysts limited their wide applications in synthesis. α,β-Unsaturated ketones are versatile synthons that were smoothly synthesized by aldol condensation or Meyer–Schuster rearrangement. The C–C double bond carbons of α,β-unsaturated ketones have been extensively applied to [2 + 2]-cycloaddition reactions. However, the [2 + 2]-cycloaddition of α,β-unsaturated ketones involving carbonyl and α-position carbons has not been reported. To our knowledge, no successful examples of the [2 + 2]-cycloaddition of α-iodo unsaturated ketones promoted by commercially available Dibal-H have been presented. Herein, we reported an efficient Dibal-H-promoted lactonization/intermolecular [2 + 2]-cycloaddition of allenic esters generated in situ from 2-(2-iodo-3,3-diphenylacryloyl)benzoates with excellent chemo- and regioselectivities under mild conditions (Scheme 1, eq 3).

Initially, the methyl 2-(2-iodo-3,3-diphenylacryloyl)benzoate (1a) was selected as the substrate to study the [2 + 2]-cycloaddition (Table 1). When 1a was treated with 1.0 equiv of

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Table 1. Initial Evaluation of the [2 + 2]-Cycloaddition Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>Dibal-H (equiv)</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>THF</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>1.05</td>
<td>THF</td>
<td>60</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>THF</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>THF</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
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<td>toluene</td>
<td>60</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>1.05</td>
<td>CICH₂CH₂Cl</td>
<td>60</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>1.05</td>
<td>1,4-dioxane</td>
<td>60</td>
<td>nr</td>
</tr>
<tr>
<td>8</td>
<td>1.05</td>
<td>THF</td>
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<tr>
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<td>THF</td>
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<td>1.05</td>
<td>THF</td>
<td>60</td>
<td>61</td>
</tr>
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</table>

“All reactions were run under the following conditions, unless otherwise indicated: substrate 1a (0.2 mmol), Dibal-H (disobutylaluminum hydride, 1 M in THF, 1.05 equiv), anhydrous solvent (2 mL) under argon atmosphere for 2 h. Isolated yield based on 1a. For 4 h.

Dibal-H (1 M in THF) in dry THF at 60 °C, to our delight, the desired cycloaddition product 2a was obtained in 67% yield (Table 1, entry 1). The structure of 2a was unambiguously confirmed by X-ray crystallographic analysis and demonstrated that the adjacent lactone functions were anti oriented (Figure 1). Increasing the amount of Dibal-H to 1.05 equiv produced 2a in 73% yield (Table 1, entry 2). Next, by increasing the dosage of Dibal-H to 1.1 equiv and 1.5 equiv, the reactions did not give better results (Table 1, entries 3 and 4). The study of the influence of different reaction media showed that toluene and CICH₂CH₂Cl were less effective (Table 1, entries 5 and 6), whereas 1,4-dioxane proved to be ineffective (Table 1, entry 7). Additionally, no better result was obtained when the reaction temperature was varied (Table 1, entries 8 and 9). Prolonging the reaction time to 4 h decreased the yield to 61% (Table 1, entry 10). Finally, the optimum conditions identified in terms of practicality and efficiency are the following: the use of 1.05 equiv of Dibal-H in anhydrous THF at 60 °C for 2 h.

Under the optimal conditions, various α-iodo-unsaturated ketones were synthesized to investigate the generality of the Dibal-H-mediated intermolecular [2 + 2]-cycloaddition, and the results are summarized in Scheme 2. This intermolecular dimerization showed high functional group tolerance and proved to be a concise methodology for the preparation of dimethylenecyclobutanes with excellent regioselectivities. First, the reactions of substrates 1b–d, possessing benzyl, ethyl, and isopropyl substituents on R¹ were performed. Compounds 1b and 1c generated the desired product 2a smoothly in moderate yields. However, the reaction of 1d provided 2a in low yield. Subsequently, we examined the electronic effects of the substituents on R² of the aromatic ring. Electron-donating substituents such as 5- or 6-methyl and 5-methoxy gave the corresponding products 2e, 2f, and 2g in 71%, 53%, and 64% yield, respectively. Substrates 1h–n, with a halo group on the aromatic ring, were also well tolerable under the standard conditions, producing the desired products 2h–n in moderate yields. Variation in the position of the halo substituents from C-4 to C-5 on the aromatic ring decreased the yields of products (2k and 2l). Moreover, electron-withdrawing groups, containing 4- or 5-nitro, were compatible in the cycloaddition, but their efficiency was unsatisfactory. Reactions with compounds 1q, 1r, 1s, and 1t bearing 4-methyl, 4-methoxy, 4-chloro, and 4-fluoro groups proceeded smoothly to furnish the corresponding adduct 2q, 2r, 2s, and 2t in good yields.

To further explore the mechanism of this intermolecular [2 + 2]-cycloaddition reaction, inhibition experiments were carried out (Scheme 3). When 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) or 2,6-di-tert-butyl-4-methylphenol (BHT) was added, the [2 + 2]-cycloaddition reaction of 1a was found to be inhibited. These results indicated that the [2 + 2]-cycloaddition of α-iodo-unsaturated ketones involves a collaborative process rather than a radical one. Furthermore, when 3-(2,2-diphenylinyl)isobenzofuran-1-one (3) was sub-

Figure 1. X-ray structure of 2a.
cycloaddition reaction. Initially, in the presence of disobutyldimethoxyaluminum hydride ((i-Bu)_2AlH), the reduction reaction of the carbonyl of α-iodo-unsaturated ketone 1a is followed by lactonization to afford the alkynyl iodo intermediate B along with a disobutyldimethoxyaluminum ((i-Bu)_2AlOMe). Subsequently, (i-Bu)_2AlOMe as base promotes the trans elimination of hydrogen with iodine groups on B to generate the allenic ester intermediate C. Finally, the intermolecularly converted cycloaddition of C is achieved to form dimethylenecyclobutanes 2a in a head-to-head manner. There are two plausible reasons to explain the obtained product regioselectivities: (1) the greater electron-donating ability of the lactone and (2) the sterical hindrance between phenyl and lactone in a head-to-tail manner.

In summary, we have developed a Dibal-H-promoted strategy for the highly selective construction of polysubstituted dimethylenecyclobutanes from readily available α-iodo-unsaturated ketones with high regioselectivity. This cycloaddition involves the cleavage of C–O and C–I bonds and the formation of two C=C bonds. Further mechanistic studies and applications of this Dibal-H-promoted lactonization/[2 + 2]-cycloaddition strategy are in progress.

**REFERENCES**


(11) CCDC 1422313 (2a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.