Synthesis of (2-Arylethylidene)cyclobutanes by Palladium-Catalyzed Reactions of Aryl Halides with Homoallyl Alcohols Bearing a Trimethylene Group at the Allylic Position

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Synthesis of (2-Arylethyllidene)cyclobutanes by Palladium-Catalyzed Reactions of Aryl Halides with Homoallyl Alcohols Bearing a Trimethylene Group at the Allylic Position

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Abstract: Treatment of aryl bromides with homoallyl alcohols bearing a trimethylene group at the allylic position in the presence of cesium carbonate under palladium catalysis affords (2-arylethyllidene)cyclobutanes selectively. The selective formation of the alkylidencyclobutane skeleton results from regiospecific retro-allylation of the homoallyl alcohols, which accompanies the transposition of the double bonds.

Key words: Palladium, Methylenecyclobutanes, Homoallyl Alcohols, Cleavage reactions, Allylation

Alkylidencyclobutanes are interesting due to their strained skeleton and reactive double bonds and are hence useful compounds in organic synthesis.1 Uncatalyzed2 and catalyzed3 cycloaddition reactions of allenes with activated alkenes represent the most useful conventional method for the synthesis of alkylidencyclobutanes. However, the use of activated alkenes, such as acrylonitrile and styrene, limits the scope of the reactions. The Wittig alkylation reactions of cyclobutanone are usually effective, unfortunately suffering from moderate yields.4 Titanocene reagents have been used in the preparation of alkylidencyclobutanes although the strong oxophilicity of the reagents leads to limited functional group compatibility.1b,5 For those reasons, a new efficient method for constructing this intriguing strained skeleton has been awaited.

We have been interested in palladium-catalyzed reactions of aryl halides with homoallyl alcohols that result in highly regiospecific synthesis of allenes.6,7 We envisioned that the alkylation reaction of aryl halides would be applicable to the synthesis of alkylidencyclobutanes by using homoallyl alcohol 2 bearing a trimethylene group at the allylic position (Scheme 1 and Table 1). After oxidative addition (Step A), alkoxide-halide exchange between aryl/palladium halide and 2 would occur to yield aryl(alkoxy)palladium (Step B). The subsequent retro-allylation of the palladium alkoxide would afford aryl(3-trimethylene-2-propenyl)palladium regioselectively, whilst releasing benzophenone (Step C). Finally, immediate reductive elimination would lead to the regioselective synthesis of alkylidencyclobutanes without forming the regioisomer, (1-trimethylene-2-propenyl)arene (Step D). Advantageously, alcohols 2 were readily prepared in a few steps from commercially available ethyl cyclobutanecarboxylate.8

Scheme 1 Idea for Constructing Alkylidencyclobutanes

Treatment of 2-bromonaphthalene (1a) with alcohol 2a in the presence of cesium carbonate and catalytic amounts of palladium acetate and tri-4-tolylphosphine in toluene at reflux provided alkylidencyclobutane 3a in 94% yield (Table 1, entry 1). Sterically demanding compounds 1b and 1c also participated in the reaction (entries 2 and 3), as did electron-deficient aryl bromides 1f and 1g, which reacted smoothly to afford the corresponding products in excellent yields (entries 6 and 7). The reaction of aryl bromide 1h, bearing an electron-donating 4-methoxy group provided 3h in 66% yield (entry 8). Carbon–carbon bond formation took place predominantly at the brominated carbon of 1i, leaving the chloro moiety intact (entry 9). The reaction of ethyl 2-bromobenzoate (1j) gave rise to a modest yield of product 3j (entry 10). The reactions of 3,5-dimethylbromobenzene (1d) and 2-bromoanisole (1k) yielded the corresponding alkylidencyclobutanes 3d and 3k, respectively, although the products were contaminated with 5% yields of regioisomers 6 (entries 4 and 11). Vinyl bromide 1l also underwent the reaction to yield the corresponding 1,4-diene (entry 12). The methyl group of 2a was not essential, since phenyl-substituted 2b as well as 2c bearing no substituents on the vinyl group also underwent the reaction (entries 13–17).
We attempted the synthesis of alkylidene cyclopropane by applying the present strategy (Table 2). However, the reaction with 7 under the standard reaction conditions was sluggish (entry 1). The rigid cyclopropane moiety of alcohol 7 would hamper the retro-allylation step probably due to the wider, fixed C(hydroxylated)-C(cyclopentyl)-C(vinyllic) angle (calculated to be 114°) compared to the calculated C(hydroxylated)-C(cyclobutyl)-C(vinyllic) angle of 2a (110°) as well as the typical unstrained C-C(sp²)-C angle (ca. 110°). The high strain-energy of methylene cyclopropane skeleton is also responsible for the difficulty. According to the literature, the strain energy of methylenecyclobutane (26.9 kcal/mol) is close to that of cyclobutane (26.5 kcal/mol). In contrast, the strain energy of methylenecyclopropane (40.9 kcal/mol) was calculated to be much larger than that of cyclopropane (27.5 kcal/mol). The retro-allylation of 7 would thus require a higher activation energy than that of 2. Heating the reaction mixture at 250 °C under microwave irradiation afforded desired product 8 exclusively, albeit in modest yield (entry 2).

Table 1 Synthesis of (2-Arylethylidene)cyclobutanes

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>1</th>
<th>R</th>
<th>2</th>
<th>3–5 time/h</th>
<th>yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-naphthyl</td>
<td>Me</td>
<td>2a</td>
<td>3a</td>
<td>13</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>1-naphthyl</td>
<td>Me</td>
<td>2a</td>
<td>3b</td>
<td>13</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>2-PhC₆H₄</td>
<td>Me</td>
<td>2a</td>
<td>3b</td>
<td>13</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>3,5-Me₂C₆H₄</td>
<td>Me</td>
<td>2a</td>
<td>3d</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4-PhC₆H₄</td>
<td>Me</td>
<td>2a</td>
<td>3e</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4-CF₂C₆H₄</td>
<td>Me</td>
<td>2a</td>
<td>3f</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-NO₂C₆H₄</td>
<td>Me</td>
<td>2a</td>
<td>3g</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4-MeOC₆H₄</td>
<td>Me</td>
<td>2a</td>
<td>3h</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4-CN(C₆H₄)</td>
<td>Me</td>
<td>2a</td>
<td>3i</td>
<td>66</td>
<td></td>
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<tr>
<td>10</td>
<td>2-NO₂C₆H₄</td>
<td>Me</td>
<td>2a</td>
<td>3l</td>
<td>53</td>
<td></td>
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<tr>
<td>11</td>
<td>2-Me₂C₆H₄</td>
<td>Ph</td>
<td>2b</td>
<td>4a</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(CH₂=CBrPh)</td>
<td>Me</td>
<td>2a</td>
<td>3k</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2-naphthyl</td>
<td>Ph</td>
<td>2b</td>
<td>4b</td>
<td>82</td>
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</tr>
<tr>
<td>14</td>
<td>4-NO₂C₆H₄</td>
<td>Ph</td>
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<td>4g</td>
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</tr>
<tr>
<td>15</td>
<td>4-MeOC₆H₄</td>
<td>Ph</td>
<td>2b</td>
<td>4h</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>2-naphthyl</td>
<td>H</td>
<td>2c</td>
<td>5a</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>4-NO₂C₆H₄</td>
<td>H</td>
<td>2c</td>
<td>5g</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

* Contaminated with regioisomer 6 (5%).

We attempted the synthesis of alkylidene cyclopropane by applying the present strategy (Table 2). However, the reaction with 7 under the standard reaction conditions was sluggish (entry 1). The rigid cyclopropane moiety of alcohol 7 would hamper the retro-allylation step probably due to the wider, fixed C(hydroxylated)-C(cyclopentyl)-C(vinyllic) angle (calculated to be 114°) compared to the calculated C(hydroxylated)-C(cyclobutyl)-C(vinyllic) angle of 2a (110°) as well as the typical unstrained C-C(sp²)-C angle (ca. 110°). The high strain-energy of methylene cyclopropane skeleton is also responsible for the difficulty. According to the literature, the strain energy of methylenecyclobutane (26.9 kcal/mol) is close to that of cyclobutane (26.5 kcal/mol). In contrast, the strain energy of methylenecyclopropane (40.9 kcal/mol) was calculated to be much larger than that of cyclopropane (27.5 kcal/mol). The retro-allylation of 7 would thus require a higher activation energy than that of 2. Heating the reaction mixture at 250 °C under microwave irradiation afforded desired product 8 exclusively, albeit in modest yield (entry 2).

Table 2 Synthesis of (2-Arylethylidene)cyclopropanes

<table>
<thead>
<tr>
<th>entry</th>
<th>heating</th>
<th>ligand</th>
<th>8/%</th>
<th>9/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>conventional, 110 °C</td>
<td>11 h</td>
<td>&lt;26</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>microwave, 250 °C</td>
<td>15 min</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>microwave, 250 °C</td>
<td>15 min</td>
<td>0</td>
<td>59</td>
</tr>
</tbody>
</table>

Interestingly, the use of trimethylphosphine instead of tri-4-tolylphosphine reversed the regioselectivity and 9 was solely obtained (entry 3). We assume that the small and electron-donating trimethylphosphine retarded the smooth reductive elimination from intermediate 10 (Scheme 2). The slow reductive elimination would lead to the isomerization of 10 to the thermodynamically more stable 11, from which reductive elimination would occur. Unfortunately, such a drastic change in regioselectivity was not observed in the reactions of 2.

Scheme 2 Isomerization of (3-Ethylene-2-methyl-2-propenyl)palladium

In summary, we have developed a new access to (2-arylethylidene)cyclobutanes, regarding the palladium-catalyzed retro-allylation of homoallyl alcohols 2 as a method for the transposition of the double bond.

Typical Procedure. Cesium carbonate (0.12 g, 0.36 mmol) was placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser. The cesium carbonate was dried in vacuo with heating with a hair dryer for 2 min. Palladium acetate (2.8 mg, 0.0125 mmol) and tri-4-tolylphosphine (15 mg, 0.050 mmol) were added to the reaction flask. The flask was then filled with argon by using the standard Schlenk techniques. Toluene (2.0 mL), homoallyl alcohol 2a (79 mg, 0.30 mmol), and 2-bromonaphthalene (1a, 52 mg, 0.25 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 13 h. After the mixture was cooled to room temperature, water (20 mL) was added. The product was extracted with hexane (20 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification with hexane as an eluent gave 2-[(2-cyclobutylidene)propynyl]naphthalene (3a, 52.0 mg, 0.234 mmol) in 94% yield. Characterization data for 3a: IR (neat) 2826, 1600, 1508 cm⁻¹; ¹H NMR (CDCl₃) δ = 1.44 (s, 3H), 1.95–2.01 (m, 2H), 2.68–2.72 (m, 2H), 2.80–2.82 (m, 2H), 3.35 (s, 2H), 7.30–7.32 (m, 1H), 7.40–7.47 (m, 2H), 7.60 (s, 1H), 7.75–7.81 (m, 3H); ¹³C NMR
(CDCl$_3$) $\delta$ 15.68, 15.86, 29.26, 29.43, 38.95, 124.83, 125.02, 125.78, 126.69, 127.42, 127.53, 127.58, 127.76, 132.02, 133.59, 134.38, 138.40. Found: C, 91.57; H, 8.06%. Calcd for C$_{17}$H$_{18}$: C, 91.84; H, 8.16%.

Acknowledgment

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References


(9) Optimized at the B3LYP/6-31G* level. For the optimized structures, see Supporting Information.

Synthesis of Alkylidencyclobutanes

\[
\begin{align*}
\text{Ar}^1 \text{Br} + \text{Ph} & \xrightarrow{\text{cat. Pd, } \text{Cs}_2\text{CO}_3, \text{toluene, } \Delta} \text{R}^2 \\
\text{Ph} & \xrightarrow{\text{OH}} \text{R}^2 \\
\end{align*}
\]