Reaction of Carboxylic Acids with Vinyl Ethers under Solvent-free Conditions Using Molecular Iodine as a Catalyst

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Abstract: The reaction of vinyl ethers with carboxylic acids using iodine as a catalyst under solvent-free conditions was investigated. The reaction of saturated carboxylic acids with vinyl ethers gave the corresponding esters. Mechanistic studies revealed the production of the adduct of the vinyl ether with the carboxylic acid, which then rearranged to form the ester. At low temperatures, the reaction of 2-(1-hydroxycyclohexyl)acetic acid (1) and butyl vinyl ether yielded a butyl ester. However, at a reaction temperature of 80°C, both the esterification and the elimination of a water molecule occurred, yielding the unsaturated butyl ester butyl 2-cyclohexenylacetate. The reaction of 2-((1S,2S,4R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetic acid (12) with butyl vinyl ether at low temperatures resulted in a mixture of four compounds. However, similar to the high-temperature (>60°C) reaction of 1, the esterification was accompanied by the elimination of a water molecule to give the unsaturated butyl ester (E)-butyl 2-((1S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)acetate. While a γ-hydrogen was abstracted to form the endo-type double bond in the reaction of 1, an α-hydrogen was abstracted to form the exo-type double bond in the reaction of 12.

Key words: esterification, iodine, vinyl ether, solvent-free condition

1 INTRODUCTION

Iodine is easy to handle and has low toxicity. Thus, it has been investigated as an efficient catalyst for several organic reactions\(^1\)-\(^8\). We previously reported the reaction of 3-hydroxy acids, such as (6-hydroxyspiro[4,5]dec-6-yl)-acetic acid, using iodine\(^9\) or strong acids\(^10\),\(^11\) as catalysts to produce the propella lactone(11-oxatricyclo[4.4.3.0\(^1,6\)]tridecan-12-one). Spirolactones and bicyclic lactones were also obtained from the corresponding 3-hydroxy acids\(^9\). We have also previously reported that the reaction of 2-(1-hydroxycyclohexyl)acetic acid with butyl vinyl ether using ZnCl\(_2\) as a catalyst yielded the corresponding spiro-lactone\(^10\).

In this study, the reactions of 3-hydroxy acids, such as 2-(1-hydroxycyclohexyl)acetic acid (1) and 2-((1S,2S,4R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetic acid (12), with butyl vinyl ether (2) using iodine as a catalyst were investigated.

2 EXPERIMENTAL

2.1 General

Melting points were measured on a Shibata micro melting point apparatus, and were uncorrected. NMR spectra were obtained using 400 or 300 MHz FT-NMR spectrometers(JEOL JNM-LA-400 or Bruker DPX-300) with Me\(_4\)Si as an internal standard and CDCl\(_3\) as a solvent. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS-HX110A, a SHIMADZU GCMS-QP5050A, or a Thermo Fisher Exactive spectrometer.

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2.2 Materials
2-(1-Hydroxycyclohexyl)acetic acid (1) and 2-((15,23,4R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetic acid (12) were prepared from the corresponding ketones as previously reported\(^1\)\(^{-15}\). The other carboxylic acids and vinyl ethers were commercially available, and they were used as received.

2.3 Esterification of 3-hydroxy acids with vinyl ether
The typical procedure is as follows (entry 11 in Table 5): 12 (0.212 g, 1.0 mmol), 2 (0.300 g, 3.0 mmol), and iodine (0.0508 g, 0.20 mmol) were placed in a reaction tube, and the mixture was stirred at 80°C for 7 h. A 5% aqueous solution of sodium thiosulfate (10 mL) was added to the reaction mixture in order to remove iodine, and the mixture was then extracted three times with 10 mL of diisopropyl ether. The organic layer was washed twice with 10 mL of saturated aqueous sodium chloride, dried with anhydrous sodium sulfate, and evaporated. The product was purified by column chromatography eluted with hexane/ethyl acetate (50/1). A total of 0.235 g (0.94 mmol; 94% yield) of an unsaturated ester (14) was obtained. The GC-MS purities of all products were above 98%.

2.4 Production of adduct (11) from hexanoic acid (8) and butyl vinyl ether (2)
The typical procedure is as follows (entry 8 in Table 3): hexanoic acid (8) (4.647 g, 40.0 mmol) and butyl vinyl ether (2) (12.02 g, 120 mmol) were placed into a 100 mL flask, and the flask was sealed. The mixture was stirred at 80°C for 6 h. The reaction mixture was washed twice with 30 mL of saturated aqueous sodium chloride, dried with anhydrous sodium sulfate, and evaporated. The product 1-butoxyethyl hexanoate (11) was purified by distillation under reduced pressure (9.3 mmHg, 148.5°C).

2.5 Rearrangement of adduct (11) to ester (9)
The typical procedure is as follows (entry 5 in Table 4): 11 (216 mg, 1.0 mmol) and iodine (50.8 mg, 0.20 mmol) were placed in a reaction tube, and the mixture was stirred at 50°C for 6 h. A 5% aqueous solution of sodium thiosulfate (10 mL) was added to the reaction mixture in order to remove iodine. The mixture was then extracted three times with 20 mL of diisopropyl ether. The organic layer was washed twice with 20 mL of saturated aqueous sodium chloride, dried with anhydrous sodium sulfate, and evaporated. The product was purified by column chromatography eluted with hexane/ethyl acetate (100/1). A total of 0.119 g (0.69 mmol; 69% yield) of 9 was obtained.

2.6 Spectroscopic data of the products
Butyl 2-(1-hydroxycyclohexyl)acetate (3)
\(^1\)H-NMR (δ, CDCl₃): 0.94 (3H, t, J = 7.3 Hz), 1.23-1.85 (14H, m), 2.47 (2H, s), 3.46 (1H, s), 4.12 (2H, t, J = 6.7 Hz);
\(^13\)C-NMR (δ, CDCl₃): 14.1, 14.5, 19.6, 23.0, 25.4, 29.4, 29.5, 31.1, 32.1, 34.8, 64.5, 174.5; IR (neat, cm\(^{-1}\)): 3510, 1716; EI-MS m/z (rel intensity): 214 (M\(^+\), 4)

Butyl 2-cyclohexenylacetate (4)
\(^1\)H-NMR (δ, CDCl₃): 0.93 (3H, t, J = 7.3 Hz), 1.38 (2H, sext, J = 7.4 Hz), 1.52-1.68 (6H, m), 2.00-2.02 (4H, m), 2.94 (2H, s), 4.08 (2H, t, J = 6.6 Hz), 5.56-6.60 (1H, m); \(^13\)C-NMR (δ, CDCl₃): 14.1, 19.5, 22.4, 23.1, 25.7, 28.8, 31.1, 44.1, 64.8, 126.0, 131.6, 172.6; IR (neat, cm\(^{-1}\)): 1736; EI-MS m/z (rel intensity): 196 (M\(^+\), 14)

Butyl nonanoate (7a)
\(^1\)H-NMR (δ, CDCl₃): 0.93 (3H, t, J = 6.8 Hz), 0.88 (3H, t, J = 6.7 Hz), 1.24-1.32 (10H, m), 1.38 (2H, quin, J = 7.4 Hz), 1.56-1.65 (4H, m), 2.29 (2H, t, J = 7.5 Hz), 4.07 (2H, t, J = 6.6 Hz);
\(^13\)C-NMR (δ, CDCl₃): 14.12, 14.50, 19.56, 23.05, 29.54, 29.57, 29.63, 31.11, 32.21, 34.82, 64.51, 174.5; IR (neat, cm\(^{-1}\)): 1739

Butyl hex-3-enoate (7b)
\(^1\)H-NMR (δ, CDCl₃): 0.93 (3H, t, J = 7.3 Hz), 0.99 (3H, t, J = 7.4 Hz), 1.38 (2H, sext, J = 7.4 Hz), 1.61 (2H, quin, J = 7.1 Hz), 2.00-2.10 (2H, m), 3.02 (2H, d, J = 6.4 Hz), 4.08 (2H, t, J = 6.7 Hz), 5.47-5.65 (2H, m);
\(^13\)C-NMR (δ, CDCl₃): 13.87, 14.12, 19.52, 25.92, 31.05, 38.55, 64.85, 121.10, 136.64, 172.78; IR (neat, cm\(^{-1}\)): 1739

Butyl cyclohexanecarboxylate (7c)
\(^1\)H-NMR (δ, CDCl₃): 0.93 (3H, t, J = 7.3 Hz), 1.18-1.92 (14H, m), 2.28 (1H, tt, J = 3.6, 11.2 Hz), 4.06 (2H, t, J = 6.6 Hz);
\(^13\)C-NMR (δ, CDCl₃): 14.14, 19.57, 25.88, 26.19, 29.46, 31.14, 43.70, 64.31, 176.68; IR (neat, cm\(^{-1}\)): 1734

Butyl 1-adamantanecarboxylate (7d)
\(^1\)H-NMR (δ, CDCl₃): 0.93 (3H, t, J = 7.3 Hz), 1.38 (2H, sext, J = 7.4 Hz), 1.60 (2H, quin, J = 7.1 Hz), 1.71 (6H, s), 1.89 (6H, s), 2.01 (3H, s), 4.05 (J = 6.5 Hz);
\(^13\)C-NMR (δ, CDCl₃): 14.16, 19.59, 28.39, 31.14, 36.95, 39.27, 41.11, 64.31, 178.25; IR (neat, cm\(^{-1}\)): 1726

Butyl benzoate (7e)
\(^1\)H-NMR (δ, CDCl₃): 0.98 (3H, t, J = 7.4 Hz), 1.48 (2H, sext, J = 7.4 Hz), 1.76 (2H, quin, J = 7.1 Hz), 4.33 (2H, t, J = 6.6 Hz), 7.44 (2H, t, J = 7.4 Hz), 7.55 (1H, t, J = 7.4 Hz), 8.05 (2H, d, J = 7.1 Hz);
\(^13\)C-NMR (δ, CDCl₃): 14.18, 19.69, 31.17, 65.25, 128.72, 129.93, 130.91, 133.20, 167.12; IR (neat, cm\(^{-1}\)): 1720

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1 H- NMR (δ, CDCl3): 0.88 (3H, t, J = 6.9 Hz), 0.95 (3H, t, J = 7.3 Hz), 1.26-1.37 (6H, m), 1.58-1.63 (4H, m), 2.29 (2H, t, J = 7.6 Hz), 4.07 (2H, t, J = 6.7 Hz); 13C-NMR (δ, CDCl3): 14.1, 14.3, 19.6, 22.7, 25.1, 31.1, 31.7, 34.8, 65.4, 174.4; IR (neat, cm−1): 1738; EI-MS m/z (rel intensity): 172 (M+, 0.1)

1-Butoxyethyl hexanoate (9)  
1 H-NMR (δ, CDCl3): 0.88-0.94 (6H, m), 1.29-1.43 (9H, m), 1.51-1.69 (4H, m), 2.32 (2H, t, J = 7.7 Hz), 3.43-3.68 (2H, m), 5.93 (1H, q, J = 5.2 Hz); 13C-NMR (δ, CDCl3): 13.8, 13.9, 19.1, 20.8, 22.3, 24.6, 31.3, 31.5, 34.6, 68.9, 96.2, 173.6; IR (neat, cm−1): 2959, 1735; b.p.: 148.5°C/9.3 mmHg; Anal. Calcd for C12H24O3: C, 66.61; H, 11.19. Found: C, 66.34; H, 11.44.

Butyl 2-((1S,2S,4R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetate (13)  
1 H-NMR (δ, CDCl3): 0.84, 0.85 (6H, each-s), 0.94 (3H, t, J = 7.3 Hz), 1.12 (3H, s), 1.28-1.49 (5H, m), 1.59-1.75 (6H, m), 2.12 (1H, dt, J = 13.3, 3.8 Hz), 2.54 (2H, dd, J = 27.5, 15.3 Hz), 3.73 (1H, s), 4.12 (2H, t, J = 6.7 Hz); 13C-NMR (δ, CDCl3): 10.6, 13.7, 19.1, 21.0, 21.4, 26.9, 30.5, 30.6, 43.1, 44.9, 46.8, 49.2, 52.3, 64.6, 79.2, 174.0; IR (neat, cm−1): 3504, 2959, 1715; EI-MS m/z (rel intensity): 268 (M+, 4); HRMS (ESI-MS) m/z calcld for C16H28O3: M+, 273.2193, found 273.2194.

(E)-Butyl 2-((1S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)acetate (14)  
1 H-NMR (δ, CDCl3): 0.74 (3H, s), 0.92-0.97 (9H, m), 1.16-1.29 (2H, m), 1.41 (2H, sext, J = 7.4 Hz), 1.59-1.88 (5H, m), 2.39 (1H, dd, J = 19.1, 2.2 Hz), 2.80-2.86 (1H, m), 4.09 (2H, t, J = 6.6 Hz), 5.58 (1H, t, J = 2.3 Hz); 13C-NMR (δ, CDCl3): 12.5, 13.7, 18.8, 19.2, 19.6, 27.3, 30.8, 34.1, 38.4, 44.4, 48.0, 53.6, 63.4, 108.0, 167.5, 175.2; IR (neat, cm−1): 2956, 1713, 1653; EI-MS m/z (rel intensity): 250 (M+, 33); HRMS (ESI-MS) m/z calcld for C25H26O3 + Na: 273.1825, found 273.1813.

Butyl 2-((1R,4R)-3,3-dimethyl-2-methylenebicyclo[2.2.1]-heptan-1-yl)acetate (15)  
1 H-NMR (δ, CDCl3): 0.93 (3H, t, J = 7.3 Hz), 1.03 (3H, s), 1.08 (3H, s), 1.16-1.28 (1H, m), 1.32-1.86 (10H, m), 2.61 (2H, d, J = 1.4 Hz), 4.07 (2H, t, J = 6.7 Hz), 4.60 (2H, d, J = 8.8 Hz); 13C-NMR (δ, CDCl3): 13.7, 19.2, 24.8, 26.0, 29.5, 30.7, 33.6, 37.5, 41.7, 43.0, 46.9, 51.2, 64.0, 98.1, 167.1, 172.5; IR (neat, cm−1): 2959, 1735; EI-MS m/z (rel intensity): 250 (M+, 34); HRMS (ESI-MS) m/z calcld for C25H28O3 + Na: 273.1825, found 273.1819.

(1S, 5R)-5,6,6-Trimethyl-4-oxatricyloc[5.2.1.01,5]decan-3-one (16)  
1 H-NMR (δ, CDCl3): 1.03 (3H, s), 1.07 (3H, s), 1.17 (3H, s), 1.28 (1H, dd, J = 10.2, 1.5 Hz), 1.39-1.48 (1H, m), 1.51-1.63 (2H, m), 1.66-1.76 (1H, m), 1.79-1.82 (1H, m), 1.87-1.92 (1H, m), 2.46 (1H, d, J = 17.3 Hz), 2.59 (1H, d, J = 17.3 Hz); 13C-NMR (δ, CDCl3): 17.8, 22.4, 23.8, 24.5, 24.7, 34.5, 39.7, 44.9, 48.5, 55.6, 95.2, 176.5; IR (KBr, cm−1): 2960, 1765; [α]D 25°: −95.8 (c = 1.24, CHCl3); m.p.: 125.5-126.5°C; EI-MS m/z (rel intensity): 194 (M+, 5).

**3 Results and discussion**

Spectroscopic data of the purified, isolated product indicated the structure of the ester, butyl 2-(1-hydroxy cyclohexyl)acetate (3). This was unexpected because we previously reported that the same reaction of 1 with 2 using zinc dichloride, instead of iodine, as a catalyst afforded the corresponding spiranolactone (2-methyl-1,3-dioxaspiro[5.5]-undecan-4-one) by intermolecular dehydration[46]. Several methods for esterification using iodine as a catalyst have been reported[15-20]. However, to the best of our knowledge, there are no reports of esterification of a carboxylic acid with a vinyl ether by using any other catalyst.

The optimum conditions for the reaction of 1 and 2 were investigated. The results are shown in Table 1. First, the amount of the catalyst (iodine) was varied when the molar ratio of 1 to 2 was 1:1.5 (entries 1-3). When the molar ratio of 1 to iodine increased from 1:0.1 (entry 1) to 1:0.2 (entry 2), the yield of ester (3) increased from 50% to 67%. However, when the molar ratio was further increased to 1:0.5, the yield decreased slightly to 64% (entry 3). When the atmosphere of the reaction system was changed from nitrogen to air (entry 4), the yield was improved dramatically to 78%. This suggests that hydrogen iodide, formed by the reaction of iodine and water in air, may act as the effective catalyst. The molar ratio of 1 to 2 was studied next. When the molar ratio was 1:3 (entry 6), the esterification proceeded almost quantitatively, improving the yield...
using reaction conditions of entry 6, the reaction temperature was increased from room temperature to 80°C (entry 8). The yield of ester 3 was dramatically decreased to 19%. However, the formation of another product was observed. The spectroscopic data indicated that the new product was the unsaturated ester, butyl 2-cyclohexenylacetate 4. This implies that not only the esterification but also the elimination of a water molecule proceeded at the higher temperature. The production of 4 was not observed in the reactions at room temperature (entries 1-6). The re-

### Table 1 Solvent-free esterification of 3-hydroxy acid 1 with butyl vinyl ether 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2 (eq.)</th>
<th>Iodine (eq.)</th>
<th>Temp. (°C)</th>
<th>Atmosphere</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>0.1</td>
<td>r.t.¹</td>
<td>N₂</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>0.2</td>
<td>r.t.</td>
<td>N₂</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>0.5</td>
<td>r.t.</td>
<td>N₂</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>0.2</td>
<td>r.t.</td>
<td>Open air</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>0.2</td>
<td>r.t.</td>
<td>Open air</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>3.0</td>
<td>0.2</td>
<td>r.t.</td>
<td>Open air</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>3.0</td>
<td>0.1</td>
<td>80</td>
<td>Open air</td>
<td>76⁶</td>
</tr>
<tr>
<td>8</td>
<td>3.0</td>
<td>0.2</td>
<td>80</td>
<td>Open air</td>
<td>19⁷</td>
</tr>
</tbody>
</table>

Reaction conditions: 1 1.0 mmol, reaction time 6 h.

¹ Room temperature.

³ Butyl 2-cyclohexenylacetate 4 was obtained in 20% yield.

⁷ Butyl 2-cyclohexenylacetate 4 was obtained in 75% yield.

### Table 2 Solvent-free esterification of carboxylic acids 5 with vinyl ethers 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹ in 5</th>
<th>R² in 6</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pentyl (8)</td>
<td>butyl (2)</td>
<td>50</td>
<td>95 (9)</td>
</tr>
<tr>
<td>2</td>
<td>octyl (5a)</td>
<td>butyl (2)</td>
<td>50</td>
<td>99 (7a)</td>
</tr>
<tr>
<td>3</td>
<td>2-pentenyl (5b)</td>
<td>butyl (2)</td>
<td>50</td>
<td>94 (7b)</td>
</tr>
<tr>
<td>4</td>
<td>cyclohexyl (5c)</td>
<td>butyl (2)</td>
<td>50</td>
<td>91 (7c)</td>
</tr>
<tr>
<td>5</td>
<td>1-adamantyl (5d)</td>
<td>butyl (2)</td>
<td>50</td>
<td>33 (7d)</td>
</tr>
<tr>
<td>6</td>
<td>1-adamantyl (5d)</td>
<td>butyl (2)</td>
<td>80</td>
<td>93 (7d)</td>
</tr>
<tr>
<td>7</td>
<td>phenyl (5e)</td>
<td>butyl (2)</td>
<td>50</td>
<td>39 (7e)</td>
</tr>
<tr>
<td>8</td>
<td>phenyl (5e)</td>
<td>butyl (2)</td>
<td>80</td>
<td>81 (7e)</td>
</tr>
<tr>
<td>9</td>
<td>heptyl (10)</td>
<td>ethyl (6a)</td>
<td>50</td>
<td>87 (7f)</td>
</tr>
<tr>
<td>10</td>
<td>heptyl (10)</td>
<td>dodecyl (6b)</td>
<td>50</td>
<td>99 (7g)</td>
</tr>
</tbody>
</table>

Reaction conditions: carboxylic acid 1.0 mmol, vinyl ether 3.0 mmol, iodine 0.20 mmol, time 6 h, open air.
Reaction mechanism of the elimination is proposed to be as follows. The conformation of the cyclohexane ring of ester 3 is considered to be a stable chair conformation. Accordingly, a $\gamma$-hydrogen lies on the same plane as the hydroxyl group. E2 elimination by an acidic catalyst may proceed readily, as shown in Scheme 1. Hydrogen iodide, formed by the reaction of iodine and water in air, is considered to act as the acidic catalyst.

Various carboxylic acids were reacted with vinyl ethers. The results are shown in Table 2. The model reaction was carried out using hexanoic acid 8 and 2 (entry 1). The reaction caused esterification, and the corresponding ester (butyl hexanoate, 9) was obtained almost quantitatively. Similar reactions were also attempted with the other carboxylic acids. Except for entries 5 and 7, the reactions proceeded smoothly to obtain the corresponding esters. In the case of entry 5, 1-adamantylcarboxylic acid (5d) was reacted with butyl vinyl ether (2) at 50°C to give butyl 1-adamantanecarboxylate (7d) in 33% yield (entry 5). Similarly, butyl benzoate (7e) was obtained in 39% yield from the reaction of benzoic acid (5e) with butyl vinyl ether (entry 7).

However, in both reactions, when the reaction temperature was raised to 80°C, the yields improved dramatically to 93% (entry 6) or 81% (entry 8).

There are two possible routes for this esterification reaction to occur, as shown in Scheme 2. One route is the formation of the alcohol from the vinyl ether, followed by esterification (Path A). The other route is the formation of the adduct followed by rearrangement (Path B). In order to investigate this reaction mechanism, hexanoic acid 8 was reacted with 2 without iodine. The results are summarized in Table 3. First, the reaction was carried out at a 1:3 molar ratio of 8 to 2. The reaction did not proceed at room temperature (entry 1). Accordingly, the reaction temperature was raised to 50°C (entry 2). From the spectroscopic data, the product was identified as the adduct of butyl vinyl ether to hexanoic acid, 1-butoxyethyl hexanoate 11. The yield was 48%. When the reaction temperature was further raised to 80°C (entry 4), the yield of 11 increased to 85%. Moreover, when the reaction time was lengthened from 3 h to 6 h (entry 8), 11 was obtained quantitatively. However, increasing the reaction time further caused a decrease in the yield of 11 (entry 9). When the molar ratio of 8 to 2 was changed from 0.33:1 to 1:4 (entries 4, 10-13), the yield was highest at the molar ratio of 1:3 (entry 4). Thus, the reaction of the carboxylic acid with butyl vinyl ether without iodine produced the adduct of the ester and the acid.

The iodine-catalyzed rearrangement of 11 using iodine as a catalyst was performed. The results are shown in Table 4. The reaction was carried out at room temperature for 6 h in an ampule (entry 1). The rearrangement of 11 afforded 9 in 28% yield. When the reaction was performed under open air at the same conditions, the yield of the ester was improved to 35% (entry 2). When the reaction temperature was raised to 50°C, the rearrangement proceeded smoothly.
The yield was highest in open air at 69% (entry 5). It is most likely that water in the air may react with iodine to form hydrogen iodide, which then acts as a catalyst. From the observations that the reaction of the carboxylic acid with butyl vinyl ether afforded the adduct, which then underwent rearrangement to give the ester, the reaction mechanism of the esterification of the carboxylic acid with butyl vinyl ether was considered to be Path B in Scheme 2. The reaction mechanism is shown in detail in Scheme 3. First, iodine reacts with carboxylic acid or water to form hydrogen iodide, which protonates the vinyl ether to form the cation. The nucleophilic attack of a proton pair from the carbonyl oxygen atom on the cation occurs, producing the adduct. An oxygen atom in the car-
bonyl group of the adduct is then protonated by hydrogen iodide, followed by elimination of acetalddehyde. Next, the iodide anion extracts a proton to form the ester. Acetaldehyde was not detected due to its low boiling point. As mentioned above, water is considered to play a role in the production of hydrogen iodide, which promotes the esterification. However, when the reaction was carried out in the absence of water, the yield of the ester decreased only slightly (entries 4, 6 and 7). The reason for this is unclear.

This esterification was applied to a terpenic 3-hydroxy acid. 12 derived from (+)-camphor was used. The results are illustrated in Table 5. When the reaction was carried out at room temperature (entry 1), the product was a mixture of four compounds: an ester (13), unsaturated esters (14 and 15), and a lactone (16). 16 was obtained by intramolecular dehydration of 12 as previously reported. However, when the reaction temperature was raised to 40°C (entry 2), 13 was not produced. When the reaction temperature was raised to 60°C (entry 4), only 14 was produced in 75% yield. When the reaction temperature was raised to 70°C or 80°C (entry 5 or 6), 14 was obtained almost quantitatively. However, although the reaction temperature was further increased (entry 7), the yield of 14 decreased. The reaction time was varied from 1 h to 7 h at 80°C (entries 6, 8-11). The yield of 14 was already 72% at the reaction time of 1 h. The effect of iodine concentration was studied when the reaction time was 6 h and reaction temperature was 80°C (entries 6, 12-15). The reaction did not proceed when iodine was not added (entry 12). At a
molar ratio of 12 to iodine of 1:0.02, a mixture of 14, 15, and 16 was obtained. However, as the molar ratio was increased to 1:0.05 (entry 14), the product was only 14 in 91% yield. Possible reaction mechanisms for the production of 14 and 15 are shown in Schemes 4 and 5, respectively. In the case of saturated ester 13, it is possible for an endo-type double bond or an exo-type double bond to have been formed by the elimination of a water molecule. However, only an exo-type double bond was formed, resulting in the formation of 14. In contrast to 3, 13 contains a rigid bornane skeleton. Thus, it is difficult for a γ-hydrogen to lie on the same plane of the hydroxyl group due to the rigidity of the bornane skeleton. Accordingly, an α-hydrogen was abstracted, resulting in the formation of an exo-type double bond. Additionally, a proton coordinated with an oxygen atom of the hydroxyl group of 12, which was followed by the elimination of a water molecule, to form a tertiary cation. Rearrangement of this cation occurred by Wagner-Meerwein rearrangement. A water molecule was then added to the resulting cation, followed by E2 elimination. The thus-formed unsaturated carboxylic acid reacted with butyl vinyl ether to give unsaturated ester 15. The mechanism involved in the production of lactone 16 was previously reported⁹.

In conclusion, the reaction of vinyl ethers with carboxylic acids using iodine as a catalyst gave the corresponding esters via the production of adducts, followed by the rearrangement. In the reaction of 2-(1-hydroxycyclohexyl)-acetic acid (1) and butyl vinyl ether, the butyl ester was obtained at low temperature. However, at a reaction temperature at 80°C, both the esterification and the elimination of water molecule occurred to afford the unsaturated ester butyl 2-cyclohexenylacetate. In the reaction of 2-(1S,2S,4R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetic acid (12) with butyl vinyl ether, a mixture of four compounds was obtained at low temperature. Similar to the reaction of 3-hydroxy acid 1, the esterification was accompanied by the elimination of a water molecule to give

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Iodine (eq.)</th>
<th>Yield (%)</th>
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</thead>
<tbody>
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<td>6</td>
<td>0.2</td>
<td>31</td>
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<tr>
<td>2</td>
<td>40</td>
<td>6</td>
<td>0.2</td>
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<td>6</td>
<td>0.2</td>
<td>0</td>
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<td>6</td>
<td>0.2</td>
<td>0</td>
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<td>70</td>
<td>6</td>
<td>0.2</td>
<td>0</td>
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<tr>
<td>6</td>
<td>80</td>
<td>6</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>reflux</td>
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<td>0</td>
</tr>
<tr>
<td>8</td>
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<td>1</td>
<td>0.2</td>
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<tr>
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<tr>
<td>15</td>
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<td>6</td>
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</table>

Reaction conditions: 12 1.0 mmol, solvent-free, open air.

* Room temperature.

Table 5  Solvent-free reaction of 3-hydroxy acid 12 with butyl vinyl ether 2.
Reaction of carboxylic acids with vinyl ethers under solvent-free conditions using molecular iodine

![Chemical Structure](image)

the unsaturated butyl ester: (E)-butyl 2-(1S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)acetate, at a reaction temperature above 60°C. While a γ-hydrogen was abstracted to form the endo-type double bond in the reaction of 1, an α-hydrogen was abstracted to form the exo-type double bond in the reaction of 12.

**References**


13) Fujita, T.; Watanabe, S.; Suga, K.; Higuchi, Y.; Sotogu-


18) Ren, Y.; Cai, C. Molecular iodine in ionic liquid, a green catalytic system for esterification and transesterification. \text{Synthetic Commun.} \ 40, 1670-1676 (2010).
