INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

Title: PRODUCTION OF MELONAL OR 2,6-DIMETHYLHEPT-5-ENAL VIA BAEYER-VILLIGER OXIDATION

Abstract: Disclosed is a process for the production of 2,6-dimethylhept-5-enal by Baeyer-Villiger oxidation of 3,7-dimethyl-octa-2,6-dienal in the presence of potassium peroxymonosulfate suspended in a solvent selected followed by hydrolysis.
The present invention is concerned with a novel process for the production of 2,6-dimethylhept-5-enal, also known as Melonal, which is an important, aldehydic, melon-like odorant for the fragrance industry. In particular, the present invention relates to a process for the synthesis Melonal by Bayer-Villiger oxidation of (E/Z)-3,7-dimethylocta-2,6-dienal, also known as Citral, in the presence of potassium peroxymonosulfate, via the intermediate 2,6-dimethylhepta-1,5-dien-1-yl formate.

Up to now 2,6-dimethyl-5-heptenal is industrially produced by Darzens reaction from 6-methyl-hept-5-en-2-one. This reaction requires alkylation with chloro acetic esters to glyctesters followed by hydrolysis and decarboxylation leading to the aldehyde: This approach is not atom economic as an alcohol (ROH), a chloride salt, as well as carbon dioxide is eliminated from the reactants.

Some years ago Corma a t al (J. Catal. 2005, 234. 96) reported a heterogeneous Baeyer-Villiger reaction of citral (1) applying zeolites and other mosoprous materials followed by hydrolysis of the intermediate formate ester. Unfortunately not only 2,6-dimethylhepta-1,5-dien-1-yl formate (2), but also olfactory disturbing side products are generated, such as 6-methylhept-5-en-2-one, citral-6,7-epoxide, citral-2,3-epoxide and various cyclization products of citral, as shown Scheme 1.

Scheme 1:

Furthermore, such heterogeneous catalysts need to be prepared in a separate process.
Accordingly, there remains a need for a simple and cheap process for the production of Melonal in an olfactory pure form.

Surprisingly, inventors found that Melonal can be prepared starting from citral by Bayer-Villiger oxidation with potassium peroxymonosulfate (KHSO₅) via the intermediate 2,6-dimethylhepta-1,5-dien-1-yl formate, resulting in high yields and high purity of the reaction product.

It was found that only if a suspension of potassium peroxymonosulfate in amides, ketones with water, nitrites with water, or esters with water is used, the reaction resulted in 2,6-dimethylhepta-1,5-dien-1-yl formate in high yields and high purity of the reaction product.

Thus there is provided in a first aspect a process comprising the oxidation of 3,7-dimethylocta-2,6-dienal (1) in the presence of potassium peroxymonosulfate suspended in a solvent selected from amides, such as N,N-dimethyl formamide (DMF), N,N-dimethyl acetamide (DMAC), N-methylpyrrolidone (NMP), ketones with about 0.5 to 5 equivalents of water (e.g. 1.5 equivalents of water), such as acetone with 0.5-5.0 equivalent of water (e.g. 1.5 equivalents of water), esters with about 0.5 to 5 equivalents of water (e.g. 1.5 equivalents of water), such as ethyl acetate with 0.5-5.0 equivalent of water (e.g. 1.5 equivalents of water), and nitriles with about 0.5 to 5 equivalents of water (e.g. 1.5 equivalents of water), such as acetonitrile with 0.5-5.0 equivalent of water (e.g. 1.5 equivalents of water), resulting in 2,6-dimethylhepta-1,5-dien-1-yl formate (2). In a subsequent step the formate (2) is hydrolyzed to melonal (I).

As a source of potassium peroxymonosulfate (KHSO₅) one may use the triple salt with the formula 2KHSO₅·KHSO₅·K₂SO₄ (MW 615), which is, e.g., commercially available under the trade name Oxone®. Preferably about 1-3 equivalents of KHSO₅ (or 0.5-1.5 equivalents of Oxone®) based on the substrate (1) are used. The potassium...
peroxymonsulfate is either added at once in form of a suspension or part of the potassium peroxymonsulfate may be successively added to the reaction.

In one embodiment the amount of potassium peroxymonsulfate is at least 0.6 equivalents of Oxone® suspended in an amide solvent, such as such as N,N-dimethyl formamide (DMF), N,N-dimethyl acetamide (DMAC), N-methylpyrrolidinone (NMP).

As is well established, by "equivalent(s)" or "eq." is meant mol equivalents based on the substrate (3,7-dimethylocta-2,6-dienal (1)).

The reactions may be carried out at different temperatures, preferably from about 0°C to about 60°C, e.g. at room temperature or at about 10°C to about 40°C.

The invention is now further described with reference to the following non-limiting examples. These examples are for the purpose of illustration only and it is understood that variations and modifications can be made by one skilled in the art.

All products described in the examples were obtained starting from (E/Z)-3,7-dimethylocta-2,6-dienal (1). The first reaction product of the Baeyer-Villiger reaction, 2,6-dimethylhepta-1,5-dien-1-yl formate (2), is a mixture of E/Z isomers.

The reported NMR spectra were measured in CDCl₃ at 300 MHz if not otherwise stated; chemical shifts (δ) are reported in ppm downfield from TMS; coupling constants J in Hz. The GC/MS analyses were run using a HB-5 column, if not stated otherwise. All purified products were purified by distillation in vacuo and isolated as colorless oils. The purity was confirmed by GC/MS.

Example 1.1: Oxone® in DMF

To the suspension of Oxone® (24.3 g, 39.5 mmol, 0.60 eq.) in DMF (70.0 ml) with a water bath at 23°C was added 3.7-dimethylocta-2,6-dienal (10.0 g, 65.7 mmol) in 10 minutes and the mixture was stirred for 90 minutes (conversion of 3,7-dimethylocta-2,6-dienal: 93%), during which time the inside temperature reached 32°C and then dropped to room temperature.
Another 4.0 g Oxone® (6.5 mmol, 0.10 eq.) was added and the mixture was stirred at 25°C for 1 hour (3,7-dimethylocta-2,6-dienal was converted completely). The mixture was filtered through a small pad of silica gel. Water (200 g) was added to the filtrate. The mixture was extracted with isohexane (3'150 mL). The combined organic phase was dried over MgSO₄ and concentrated. The residue (9.5 g) was distilled by Kugelrohr to furnish 2,6-dimethylhepta-1,5-dien-1-yl formate (7.7 g, 42.7 mmol, 65% yield) (Mixtures of E/2 isomers in a ratio of 72:28) as a colorless liquid.

\[ \text{Example 1.2:} \]

The procedure as described in Example 1.1) was repeated with varying amounts of Oxone®. The results are given in Table 2 below.

\[ \text{Example 2.1: Oxone® in DMAC} \]

To a solution of 3,7-dimethylocta-2,6-dienal (6.0 g, 39.4 mmol, 1.0 eq.) in DMAC (50 ml) was added Oxone® (19.4 g, 31.5 mmol, 0.80 eq.) in one portion. The suspension was stirred at room temperature for 90 minutes. GC analysis indicated 3,7-dimethylocta-2,6-dienal was converted completely. The mixture was filtered and the solid was washed with 100 mL petroleum ether. The filtrate was washed with water (150 mL). The aqueous phase was extracted by petroleum ether (2'150 mL). The combined organic phase was dried over MgSO₄ and concentrated, and the residue (4.2 g) was distilled by Kugelrohr distillation to furnish 2,6-dimethylhepta-1,5-dien-1-yl formate (3.6 g, 21.4 mmol, 54% yield) as a colorless liquid.

\[ \text{Example 2.2: Oxone® in NMP} \]

To the suspension of Oxone® (28.3 g, 46.0 mmol, 0.70 eq.) in NMP (70 ml) with a water bath at 23°C was added 3,7-dimethylocta-2,6-dienal (10 g, 65.7 mmol, 1.0 eq.) in 5 minutes and the mixture was stirred for 180 minutes (conversion of 3,7-dimethylocta-
2,6-dienal: 85%). Another 4.0 g Oxone® (6.5 mmol, 0.10 eq.) was added and the mixture was stirred at 2SX for 1 hour (conversion of 3,7-dimethylocta-2,6-dienal: 95%). The mixture was filtered through a small pad of silica gel. Water (2.00 g) was added to the filtrate. The mixture was extracted with isohexane (3·150 mL). The combined organic phase was dried over MgSO₄ and concentrated. The residue (9.5 g) was distilled by Kugelrohr to furnish 2,6-dimethylhepta-1,5-dien-1-yl formate (6.1 g, 33.8 mmol, 51% yield) as a colorless liquid.

Example 3.1: Oxone® in acetone

In a 250 mL three-necked round-bottomed flask was added Oxone® (33.9 g, 55.0 mmol) in acetone (80 mL) to give a white suspension. With vigorously stirring, water (1.80 g, 100 mmol) was added to the suspension. 3,7-Dimethylocta-2,6-dienal (15.2 g, 100 mmol) was added dropwise in 5 minutes. The addition was not exothermal. The slurry reaction mixture was vigorously stirred at room temperature for 4 hours. The reaction was monitored by GC. After one hour the conversion of 3,7-dimethylocta-2,6-dienal was 49% (GC selectivity = (desired product) / (desired product + all other by-products) = 88%). After 4 hours, GC conversion was 81.8% (GC selectivity = (desired product) / (desired product + all other by-products) = 82.5%). The conversion stopped and the reaction mixture was filtered and the white solid was washed with 3·10 mL acetone. The combined filtrates were tested by peroxide content test paper. The peroxide content was 10 ppm. Sodium bisulfite (5.2 g, 5.0 mmol) and water (10 mL) were added to the acetone solution. The mixture was stirred at room temperature until peroxide test indicated negative result (about 30 minutes). MgSO₄ (5.0 g) was added and the suspension was filtered. The filtrate was concentrated to give 20.0 g yellow cloudy liquid. The liquid was dissolved in MTBE (100 mL), washed once with brine (50 mL) and dried by MgSO₄. Concentration gave 17.5 g light yellow liquid. Kugelrohr distillation gave a colorless liquid (10.6 g) (boiling point: 75-85 degree/0.25 mbar). GC purity of the 2,6-dimethylhepta-1,5-dien-1-yl formate is 90% and with 1.5% of melonal and with some others are unreacted citral. Yield 57%.

Example 3.2 - 3.3:
The procedure as described in Example 3.1) was repeated with varying amounts of water. The results are given in Table 2 below.
Example A 1 Oxone ® in ethyl acetate

In a 250 mL three-necked round-bottomed flask was added Oxone ® (33.9 g, 55.0 mmol) in ethyl acetate (120 ml) to give a white suspension. With vigorously stirring, water (1.80 g, 100 mmol) was added to the suspension. 3,7-Dimethylocta-2,6-dienal (15.2 g, 100 mmol) was added dropwise in 5 min. The addition was not exothermal. The slurry reaction mixture was vigorously stirred at room temperature for 20 hours. The reaction was monitored by GC (results are given in the Table 1 below). After 20 hours additional 9.0 g, 4.0 g and 4.0 g of Oxone ® were successively added in portions to the reaction mixture within 4 hours. The reaction mixture was filtered and the filtrate was washed once with sodium bisulfite (10.4 g, 10.0 mmol) in water (80 mL). After the washing, the peroxide test paper indicated negative result. The organic phase was further washed once with brine (50 mL), dried by MgSO 4 and concentration to remove the solvent resulting in a light yellow liquid (18.0 g) of the organic phase. Kugelrohr distillation gave a colorless liquid (12.6 g). Boiling point: 75-85 degree/0.25 mbar. GC purity of the 2,6-dimethylhepta-1,5-dien-1-yl formate product is 95% and with some of melonal and unreacted citral. Yield 71%.

Table 1:

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<tr>
<th>Time</th>
<th>GC – conversion</th>
<th>GC – selectivity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour</td>
<td>10 %</td>
<td>58 %</td>
</tr>
<tr>
<td>2 hours</td>
<td>24.3 %</td>
<td>79 %</td>
</tr>
<tr>
<td>3 hours</td>
<td>38.2 %</td>
<td>85 %</td>
</tr>
<tr>
<td>20 hours</td>
<td>74.5 %</td>
<td>93 %</td>
</tr>
<tr>
<td>30 hours</td>
<td>92.0 %</td>
<td>86 %</td>
</tr>
</tbody>
</table>

* GC selectivity = (desired product) / (desired product + all other by-products)

Example 4.2:
The procedure as described in Example 4.1) was repeated in the absence of water. The results are given in Table 2 below.
Example 5:1: Oxone® in acetonitrile
In a 250 mL three-necked round-bottomed flask was added Oxone® (33.9 g, 55.0 mmol) in acetonitrile (80 ml) to give a white suspension. With vigorously stirring, water (1.80 g, 100 mmol) was added to the suspension, 3,7-Dimethylocta-2,6-dienal (15.2 g, 100 mmol) was added dropwise in 5 minutes. The slurry reaction mixture was vigorously stirred at room temperature for 4 hours. The reaction was monitored by GC. After one hour the conversion of 3,7-dimethylocta-2,6-dienal was 82%. The reaction mixture was filtered and the white solid was washed with 3 * 10 mL acetonitrile. The filtrate was concentrated to give 18.0 g yellow cloudy liquid. The liquid was dissolved in MTBE (100 mL), washed once with brine (50 mL) and dried by MgSO₄. Concentration gave 17.5 g light yellow liquid. Kugelrohr distillation gave 2,6-dimethylhepta-1,5-dien-1-yl formate as a colorless liquid (7.6 g) (boiling point: 75-85 degreeC at 25 mbar). GC purity of the 2,6-dimethylhepta-1,5-dien-1-yl formate is 80% and with some others are unreacted citral. Yield 36%.

Example 5.2:
The procedure as described in Example 5.1) was repeated in the absence of water. The results are given in Table 2 below.

Example 6 (comparison): Oxone® in methanol
Following the general procedure as described in Example 1, to the suspension of Oxone® (24.3 g, 39.5 mmol, 0.60 eq.) in methanol (70 ml) was added 3,7-dimethylocta-2,6-dienal (10 g, 65.7 mmol, 1.0 eq.) in 10 minutes and the mixture was stirred at 23°C for 120 minutes (conversion of 3,7-dimethylocta-2,6-dienal was 78%). The reaction was a very complex mixture and the GC selectivity (GC selectivity = (desired product) / (desired product + all other by-products)) of the 2,6-dimethylhepta-1,5-dien-1-yl formate was lower than 5%.
<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>Water (eq.\textsuperscript{1})</th>
<th>Oxone\textsuperscript{®} (eq.\textsuperscript{1})</th>
<th>Time (hours)</th>
<th>Conversion (%)</th>
<th>Yield (%)\textsuperscript{2}</th>
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<tr>
<td>1</td>
<td>DMF</td>
<td>-</td>
<td>0.55</td>
<td>1.0</td>
<td>79</td>
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</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>-</td>
<td>0.60</td>
<td>1.0</td>
<td>93</td>
<td>n. d.</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>-</td>
<td>0.70</td>
<td>2.5</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>DMAC</td>
<td>-</td>
<td>0.80</td>
<td>1.5</td>
<td>100</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>NMP</td>
<td>-</td>
<td>0.80</td>
<td>4.0</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Acetone</td>
<td>-</td>
<td>0.55</td>
<td>1.0</td>
<td>5.0</td>
<td>n. d.</td>
</tr>
<tr>
<td>7</td>
<td>Acetone</td>
<td>1.0</td>
<td>0.55</td>
<td>1.0</td>
<td>49</td>
<td>n. d.</td>
</tr>
<tr>
<td>8</td>
<td>Acetone</td>
<td>†:0</td>
<td>0.55</td>
<td>4.0</td>
<td>82</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>Acetone</td>
<td>10</td>
<td>0.55</td>
<td>1.0</td>
<td>90</td>
<td>&lt;10</td>
</tr>
<tr>
<td>10</td>
<td>Ethyl acetate</td>
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<td>0.55</td>
<td>2.0</td>
<td>0</td>
<td>n. d.</td>
</tr>
<tr>
<td>11</td>
<td>Ethyl acetate</td>
<td>1.0</td>
<td>0.55</td>
<td>1.0</td>
<td>10.0</td>
<td>n. d.</td>
</tr>
<tr>
<td>12</td>
<td>Ethyl acetate</td>
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<td>20</td>
<td>75</td>
<td>62</td>
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<td>13</td>
<td>Ethyl acetate</td>
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<td>0.80</td>
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<tr>
<td>14</td>
<td>CH\textsubscript{3}CN</td>
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<td>0.55</td>
<td>1.0</td>
<td>3.7</td>
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<td>CH\textsubscript{3}CN</td>
<td>1.0</td>
<td>0.55</td>
<td>1.0</td>
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<td>36</td>
</tr>
<tr>
<td>16</td>
<td>Methanol</td>
<td>-</td>
<td>0.60</td>
<td>2.0</td>
<td>78</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

\textsuperscript{1) Mol equivalents based on 3,7-dimethylocta-2,6-dienal (1)}

\textsuperscript{2) n. d. = not determined}

As can be seen from the results above, the addition of water is important for the process in solvents such as acetone, ethyl acetate and acetonitrile. But when water content is too larger (greater than 10 equivalent), the process gave poor selectivity of the desired 2,6-dimethylhepta-1,5-dien-1-yl formate product.
Example 7: Conversion of 2,6-dimethylhepta-1,5-dien-1-yl formate to melonal

The 2,6-dimethylhepta-1,5-dien-1-yl formate obtained according to one of the processes as described above was hydrolyzed using NaOH solution resulting in melonal (99% purity).
1. A process for the production of 2,6-dimethylhept-5-enal by Baeyer-Villiger oxidation of 3,7-dimethylocta-2,6-dienal in the presence of potassium peroxymonosulfate suspended in a solvent selected from amides, ketones with 0.5 - 5.0 equivalents of water, esters with 0.5 - 5.0 equivalents of water and nitriles with 0.5 - 5.0 equivalents of water, resulting in 2,6-dimethylhepta-1,5-dien-1-yl formate, followed by hydrolysis.

2. A process according to claim 1 wherein the amides are selected from N,N-diethyl formamide (DMF), N,N-dimethyl acetamide (DMAC), N-methylpyrrolidinone (NMP).

3. A process according to claim 1 wherein the ketone is acetone.

4. A process according to claim 1 wherein the ester is ethyl acetate.

5. A process according to claim 1 wherein the nitrile is acetonitrile.

6. A process according to claim 1 wherein the resulting 2,6-dimethylhepta-1,5-dien-1-yl formate is hydrolysed in the presence of NaOH.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C47/21 C07C45/54

ADD.

According to International Patent Classification (IPC) or both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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Further documents are listed in the continuation of Box C. See patent family annex.

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*A* document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

14 December 2015

Date of mailing of the international search report

12/01/2016

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