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(71) Applicant: **DSM IP ASSETS B.V.** [NL/NL]; Het Overloon 1, 6411 TE Heerlen (NL).

(72) Inventors: **BONRATH, Werner**; DSM Nutritional Products Ltd, c/o Patent Department, Wurmisweg 576, 4303 Kaiseraugst (CH). **KUENZI, Rolf**; DSM Nutritional Products Ltd, c/o Patent Department, Wurmisweg 576, 4303 Kaiseraugst (CH). **NIETO-ORTEGA, Belen**; DSM Nutritional Products Ltd, c/o Patent Department, Wurmisweg 576, 4303 Kaiseraugst (CH). **MEDLOCK, Jonathan, Alan**; DSM Nutritional Products Ltd, c/o Patent Department, Wurmisweg 576, 4303 Kaiseraugst (CH).

(74) Agent: **KURT, Manfred**; DSM Nutritional Products Ltd, Patent Department, Wurmisweg 576, 4303 Kaiseraugst (CH).

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(54) Title: PROCESS FOR ETHYNYLATING SPECIFIC ALPHA, BETA-UNSATURATED KETONES

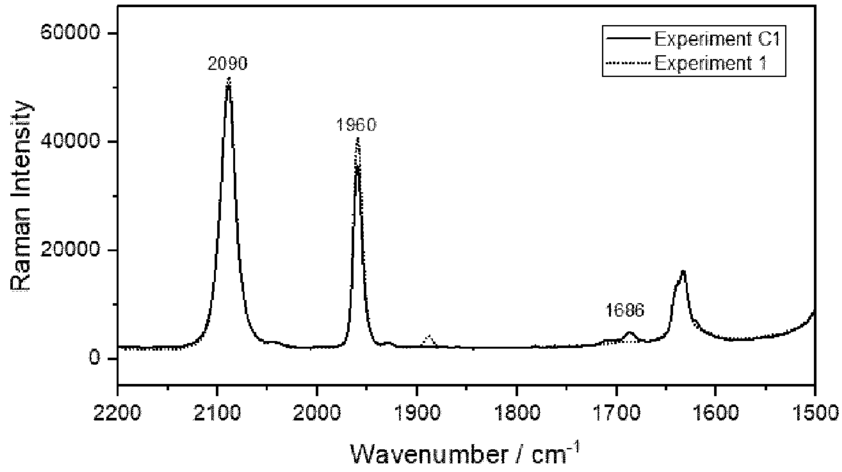

Figure 7: Raman spectra of the reactions Example 1 and C1. Example C1 contains polymer as indicated by the band at approximately 1685 cm^{-1}.

(57) **Abstract:** The present invention relates to an improved process for ethynylating specific α,β-unsaturated ketones for producing tertiary acetylenic alcohols.

[Continued on next page]

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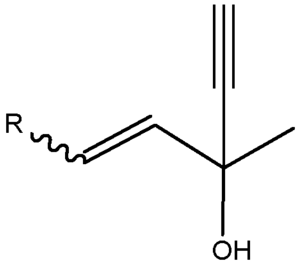
PROCESS FOR ETHYNYLATING SPECIFIC ALPHA, BETA-UNSATURATED KETONES

The present invention relates to an improved process for ethynylating specific α,β-unsaturated ketones for producing tertiary acetylenic alcohols.

The process for ethynylating α,β-unsaturated ketones for producing tertiary acetylenic alcohols is well known and has been disclosed and described in patent applications and publications. For example, in US4320236 or Chimia, 40(9), 1986 p.323 - 330 such an ethynylation is described in detail.

The present invention relates to an improved process to produce a compound of formula (I)



(I)

,

wherein R is H, an aliphatic or aromatic hydrocarbon moiety and the wavy bond means that the carbon-carbon double bond to which it is attached to, can be in the (E) or (Z) configuration.

Such compounds can be used as such, or additionally they can be used intermediates in the synthesis of other industrially relevant compounds, (for example vitamin A derivatives and carotenoids)

Due to the importance of the compounds of formula (I), there is always a need to provide improved syntheses.

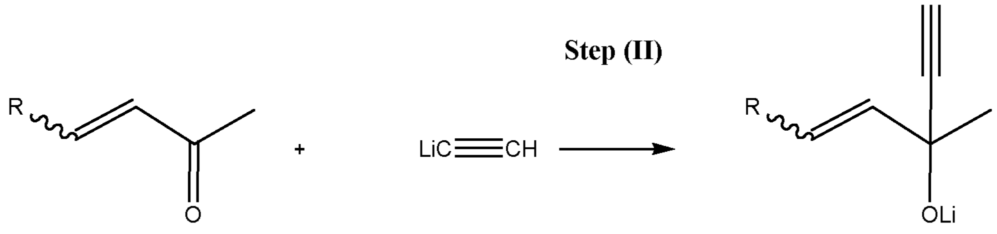
As stated above there are a few ways to produce compounds of formula (I).

According to the literature (such as US4320236 or Chimia, 40(9), 1986 p.323 - 330), the specific ethynylation can be summarized as done in the following scheme:

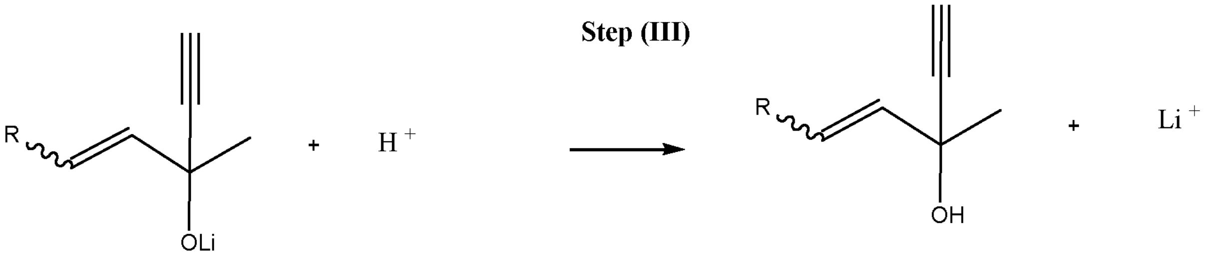
Step (I)

$$2\ \mathrm{Li} + 3\ \mathrm{HC{\equiv}CH} \xrightarrow{\mathrm{NH_3}} 2\ \mathrm{LiC{\equiv}CH} + \mathrm{H_2C{=}CH_2}$$

Step (II)



Step (III)



wherein R is as defined above and in more detail below.

Proposed by the literature mentioned above, step (I) consists of the following two steps (step (Ia) and step (Ib)):

Step (Ia)

$$2\ \mathrm{Li} + 2\ \mathrm{HC{\equiv}CH} \xrightarrow{\mathrm{NH_3}} \mathrm{LiC{\equiv}CLi} + \mathrm{H_2C{=}CH_2}$$

Step (Ib)

$$\mathrm{LiC{\equiv}CLi} + \mathrm{HC{\equiv}CH} \longrightarrow 2\ \mathrm{LiC{\equiv}CH}\ .$$

One of the main disadvantages and downsides of the process described in the prior art is the control of the process.

The processes of the prior art use the starting materials in a large excess to achieve good yield, resulting in a large amount of waste. Particularly, in the case of an excess of unsaturated ketones such as those of formula (II), oligomers and polymers can be produced which are very difficult to remove and result in a significant yield loss.

Furthermore, the correct moment of the addition of the starting material in the various steps (step (I), step (II) and step (III)) is also challenging. If the starting material is added too early or too late that can lead to unwanted side products, which then have to be removed in an time-consuming and extensive process.

In chemical reactions using the correct stoichiometry of reagents is important, the ideal situation is to only exactly the right amount of the reagent to completely consume the starting material. If an excess of one component (starting material or reagent) is used, this generally results in lower yields and higher costs due to the value of the unreacted excess. An excess of reagents can result in a more hazardous reaction mixture and so require more safety controls. In addition, the excess of this reagent has to be removed from the product, potentially requiring further expensive purification steps. Furthermore, an excess of one component can react to produce by-products, which require removal from the product. Specifically, compounds of formula (II) are known to be toxic and also susceptible to polymerization. Polymers cause significant difficulties and extra costs in their removal in purification steps. Thus, the amounts of reagents used in the reaction should be minimized and their addition to a reaction stopped as soon as the other reaction components are completely consumed.

Therefore, the goal of the present invention was to find a way and a process to produce specific tertiary acetylenic alcohols, which reduces the amount of unwanted side products.

Surprisingly, it was found when the reaction progress was monitored by using Raman spectroscopy it was possible to find the ideal point in time to add the various starting material and also to stop the reactions at the ideal moments.

Raman spectroscopy (named after Indian physicist C. V. Raman) is a non-destructive vibrational spectroscopic technique which provides exhaustive information about molecular interactions, polymorphism, crystallinity, and chemical structure in general.

Raman spectroscopy is based upon the called Raman effect, in which the incident light from a high intensity laser light source is scattered from a sample at different wavelength as laser source, which depend on the chemical structure of the sample.

Therefore, a Raman spectrum features the intensity and the wavenumber position of the scattered light which can be correlated with specific molecular bonds, allowing the identification of unknown samples, or monitoring the reaction path of the substances.

Some functional groups are more Raman active than others and will produce more intense bands. For example, the C=O bond characteristic of aldehydes is not strongly Raman-active. Alternatively, triple bonds such as C≡C are highly active.

The Raman spectroscopy can be carried by using any commonly available instrument. There are multiple producers and suppliers for Raman equipment, for example Kaiser Optical Systems, Bruker and Mettler Toledo. These instruments can be fitted with a variety of probes and optics for the analysis of liquids, solids and gases. A very suitable way to carry out the Raman spectroscopy in a chemical reaction is by using an immersion probe, which is put into the reaction mixture, inside the vessel.

The process according to present invention is carried out the following way:

In step (Ia), the lithium metal is added to NH_3, and then the ethyne (HCCH) is added forming the lithium carbide.

Step (Ia)

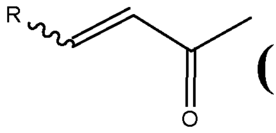
$$2\,\mathrm{Li} \quad + \quad 2\ \mathrm{HC{\equiv}CH} \xrightarrow{\mathrm{NH_3}} \mathrm{LiC{\equiv}CLi} + \mathrm{H_2C{=}CH_2}$$

Then when more ethyne (HCCH) is added (step (Ib)), the lithium carbide is converted into lithium acetylide.

Step (Ib)

$$\mathrm{LiC{\equiv}CLi} \quad + \quad \mathrm{HC{\equiv}CH} \longrightarrow 2\ \mathrm{LiC{\equiv}CH}$$

The important feature is to determine the exact point where the lithium carbide is completely converted to the lithium acetylide. At this point the addition of the ketone of formula (II) is added

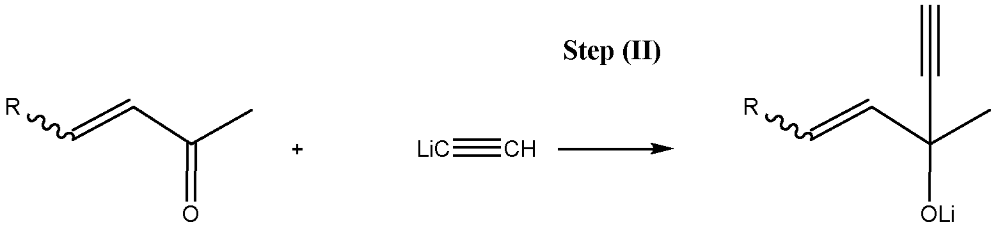


(II)

wherein R is as defined above and in more detail below.

If the addition of the ketone of formula (II) is too early or too late then a significant amount of unwanted side products is produced. Such side products have to be removed by applying a time-consuming and extensive purification process.

Furthermore, also step (II) can be controlled better by following the reaction using Raman spectroscopy:

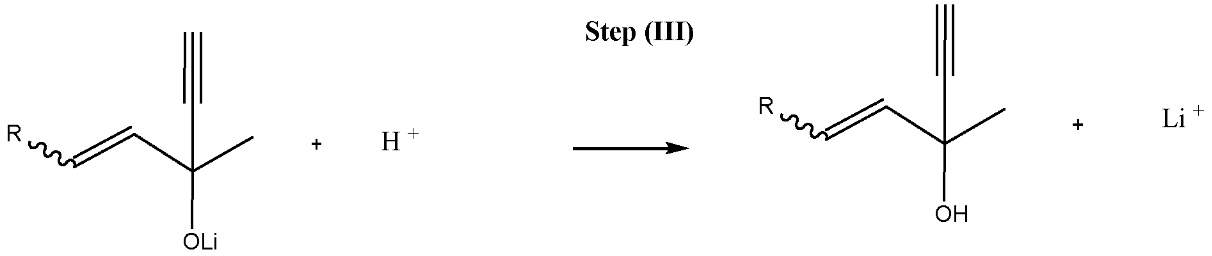


(II) (III)

wherein R is as defined above and in more detail below.

As described above, the correct point to add the ketone of formula (II) can be determined by Raman spectroscopy. Additionally, Raman spectroscopy can be used to determine when all lithium acetylide is consumed to identify the exact moment when to stop the addition of the ketone of formula (II).

In the final stage (step III))

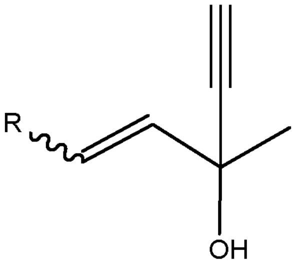


wherein R is as defined above and in more detail below,

the hydrolysis is carried out to obtain the compound of formula (I) in excellent yield. The hydrolysis of the compound of general formula (III) can be affected in a manner known per se, such as but not limited to use of Bronsted acids such as sulfuric acid, acetic acid, water, ammonium chloride.

As stated above the amount of unwanted side products and waste is reduced significantly in the overall process.

Therefore, the present invention relates to a process (P) for the production of compounds of formula (I)


(I)

,

wherein

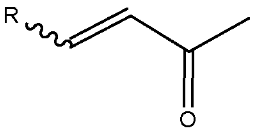
R is H; a linear, branched or cyclic C_1-C_{30} alkyl group, which can comprise ring systems and, which can be substituted with oxygen atoms; or a linear, branched or cyclic $C_2 – C_{30}$ alkylene moiety, which can comprise ring systems and, which can be substituted with oxygen atoms, wherein

a first step lithium is added to NH_3 and then

ethyne (HCCH) is added to the reaction mixture and

in a second step (step (II))

a compound of formula (II)


(II)

,

wherein

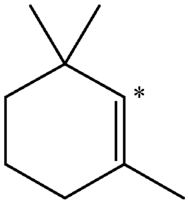
R and the wavy bond have the same meaning as defined for the compound of formula (I), and

then in a third step (step (III)) the obtained product is hydrolyzed,

characterized in that the step (I) and step (II) and optionally step (III) are controlled by monitoring the reaction progress by using Raman spectroscopy.

In a preferred embodiment of the present invention, R is H; a linear, branched or cyclic C_1-C_{15} alkyl group, which can comprise ring systems and, which can be substituted with oxygen atoms; or a linear, branched or cyclic C_1-C_{15} alkenyl group, which can comprise ring systems and, which can be substituted with oxygen atoms.

In a more preferred embodiment of the present invention, R is H; a linear or branched C_1-C_{10} alkyl group; a linear, branched or cyclic C_1-C_{15} alkenyl group, which comprise one carbon-carbon double bond; or a substituted cyclohexene ring chosen from the group consisting of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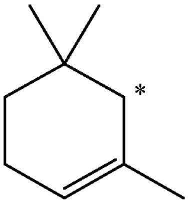
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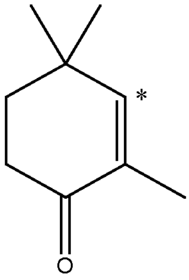
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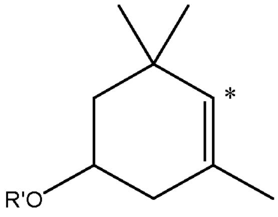
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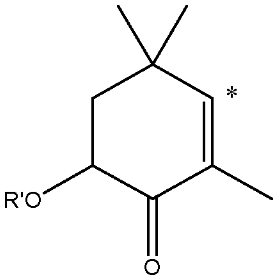
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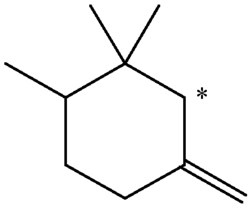
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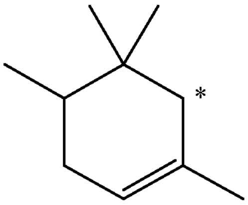
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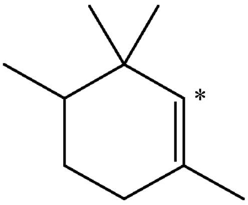
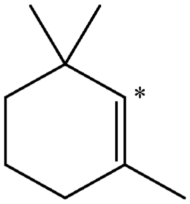

,

wherein the "*" shows the C bonding to the compound of formula (I) and compound of formula (II) and

R' is H or a C_1-C_4 alkyl group or –(CO)C_1-C_4alkyl or -C(COCH$_3$)(CH$_3$)$_2$.

In an even more preferred embodiment of the present invention, R is H; a linear or branched C_1-C_{10} alkyl group; a linear, branched or cyclic C_1-C_{15} alkenyl group, which comprise one carbon-carbon double bond; or a substituted cyclohexene ring chosen from the group consisting of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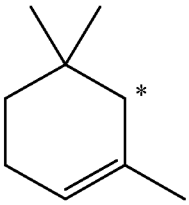
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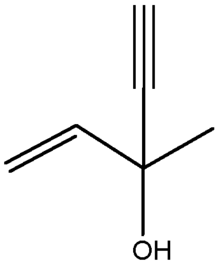
wherein the "*" shows the C bonding to the formula (I) and (II).

In a most preferred embodiment of the present invention the compound of formula (I')

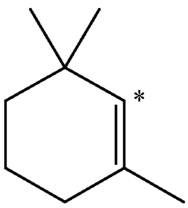


(I')

is used.

Therefore, the present invention also relates to a process (P'), which is process (P), wherein R is H; a linear, branched or cyclic C_1-C_{15} alkyl group, which can comprise ring systems and, which can be substituted with oxygen atoms; or a linear, branched or cyclic C_1-C_{15} alkenyl group, which can comprise ring systems and, which can be substituted with oxygen atoms.

Therefore, the present invention also relates to a process (P"), which is process (P), wherein R is H; a linear or branched C_1-C_{10} alkyl group; a linear, branched or cyclic C_1-C_{15} alkenyl group, which comprise one carbon-carbon double bond; or a substituted cyclohexene ring chosen from the group consisting of



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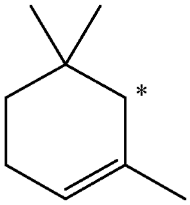

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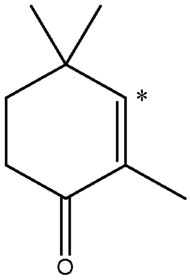

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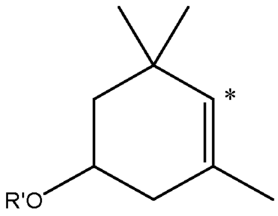

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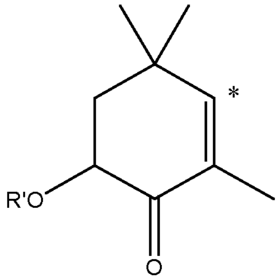

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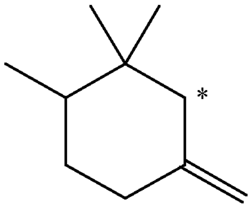

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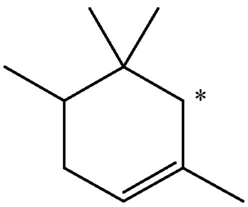

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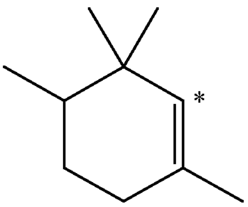

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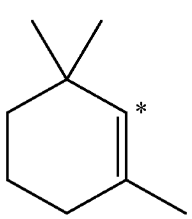
wherein the "*" shows the C bonding to the formula (I) and (II) and R' is H or a C_1-C_4 alkyl group or $–(CO)C_1$-C_4alkyl or $-C(COCH_3)(CH_3)_2$.

Therefore, the present invention also relates to a process (P'"), which is process (P), wherein

R is H; a linear or branched C_1-C_{10} alkyl group; a linear, branched or cyclic C_1-C_{15} alkenyl group, which comprise one carbon-carbon double bond; or a substituted cyclohexene ring chosen from the group consisting of



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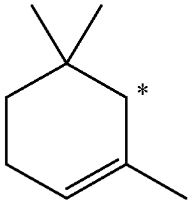

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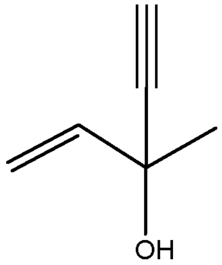
wherein the “*” shows the C bonding to the formula (I) and (II).

Therefore, the present invention also relates to a process (P’’’’), which is process (P), wherein the compound of formula (I’)

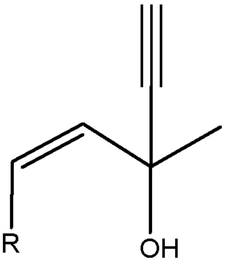


(I')

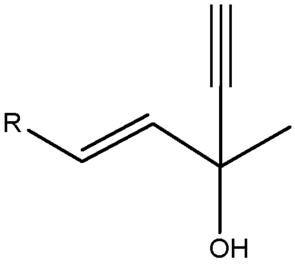
is used.

The Raman spectroscopy is used to determine when to add or when to stop adding the various reaction compounds.

As stated above the by introducing the wavy bond (in formula (I) and formula (II)), it is meant, that the compound of formula (I) can be the compound of formula (Ia) or the compound of formula (Ib)



(Ia)



(Ib)

wherein R is as defined above

as well a mixture of the compound of formula (Ia) and the compound of formula (Ib) in any ratio (R has the same meaning as defined above).

The same applies for the compound of formula (II) and of formula (III).

Any commonly known and commercially available Raman spectroscopy device can be used. Preferably an immersion probe attached to a Raman analyzer or Raman spectrometer. Such Raman devices are commercially available from a variety of producers and suppliers. Raman immersion probes can be integrated easily into the process equipment.

All values given in the present patent application are measured with a Raman spectrometer from Kaiser Optical Systems (Kaiser Raman Rxn2 analyzer). This spectrometer is equipped with a CCD detector, which allows a full Raman spectrum to be recorded in a few seconds. The 785 nm laser was used at 50 mW.

For the experiments described in the present patent, spectra were recorded every minute, with a resolution of better than 2 cm^{-1}. An exposure time of 10 seconds was used during the complete reaction time. No fluorescence effects were observed.

As stated above the exact point of the addition of the various reagents during the process is determined by Raman spectroscopy.

The reaction conditions for the ethynylation are similar to those disclosed in US4320236.

Step (I) (both steps Ia and Ib) is usually carried out at a temperature range of from -90°C to -10 °C. The lithium metal is usually added with stirring.

Therefore, the present invention also relates to a process (P1), which is process (P), (P'), (P''), (P''') or (P''''), wherein step (I) is carried out at a temperature range of from -90°C to -10 °C.

In step (Ia)

Step (Ia)

$$2\ Li + 2\ HC{\equiv}CH \xrightarrow{NH_3} LiC{\equiv}CLi + H_2C{=}CH_2$$

the Raman spectroscopy is used to determine when the lithium has first been added to the ammonia and then to monitor the formation of the lithium carbide.

At the beginning of the process according to the present invention (no lithium added to the NH_3 yet) three peaks can be seen between 3000 cm^{-1} to 3500 cm^{-1} (see Figure 1) (the N-H stretching band).

When adding the lithium to the NH_3 the three peaks between 3000 cm^{-1} to 3500 cm^{-1} disappear in this region (see Figure 2) and a shift is observed in the N-H bending bands.

After addition of the lithium is complete, the dosing of acetylene is started.

The dosing of acetylene can be followed by Raman spectroscopy. Two bands are recorded in the region of 1895 to 1865 cm^{-1}, which can be attributed to an acetylene solvated species (Figure 3).

Continuing to add acetylene, two Raman bands of the solvate species disappear and two bands, in the region of 1880 to 1835 cm^{-1}, are detected (Figure 4). In this moment, the addition of acetylene can be stopped, the lithium carbide is formed.

Raman spectroscopy indicates when the formation of lithium carbide is completed, and the addition of acetylene is stopped.

Therefore, the present invention also relates to process (P2), which is process (P), (P’), (P’’), (P’’’), (P’’’’) or (P1), wherein the dosing of acetylene is stopped when the new peaks (in the region of 1880 to 1835 cm^{-1}) appear.

At this point, at least one inert solvent is added to the reaction mixture. Suitable inert solvents for the process according to the present invention are ethers and aromatic hydrocarbon compounds, such as i.e., diethyl ether, di-n-propyl ether, diisopropyl ether, dioxane, tetrahydrofuran, 2-methyl tetrahydrofuran, benzene and toluene.

Therefore, the present invention also relates to process (P3), which is process (P), (P’), (P’’), (P’’’), (P’’’’), (P1) or (P2), wherein at least one inert solvent is added to the reaction mixture when two peaks in the region of 1880-1835 cm^{-1} are observed.

Therefore, the present invention also relates to process (P3’), which is process (P3), wherein the at least one inert solvent is chosen from the group consisting of ethers and aromatic hydrocarbon compounds.

Therefore, the present invention also relates to process (P3’’), which is process (P3), wherein the at least one inert solvent is chosen from the group consisting of diethyl ether, di-n-propyl ether, diisopropyl ether, dioxane, tetrahydrofuran, 2-methyl tetrahydrofuran, benzene and toluene.

In step (Ib), after the addition of the at least one solvent more acetylene is added to the reaction mixture:

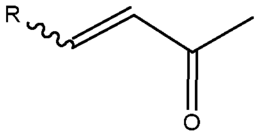
Step (Ib)

$$LiC{\equiv}CLi + HC{\equiv}CH \longrightarrow 2\ LiC{\equiv}CH.$$

After the solvent exchange (from NH_3 to the at least one inert solvent) and further addition of acetylene, the bands of the lithium carbide decrease (two bands 1880-1835 cm^{-1}) and the lithium acetylide can be detected. At this point total conversion to lithium acetylide is reached and it can be observed by Raman (band at approximately 1885 cm^{-1}) (see Figure 5).

Therefore, the present invention also relates to process (P4), which is process (P), (P'), (P''), (P'''), (P''''), (P1), (P2), (P3), (P3') or (P3''), wherein the dosing of acetylene is stopped when two peaks in the region of 1880-1835 cm^{-1} have disappeared and the peak in the region of 1885 cm^{-1} appears.

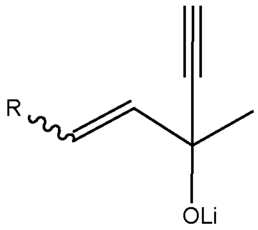
At this point (Step II), the compound of formula (II)



(II) ,

wherein
R has the same meanings as defined above,

is added to the reaction mixture and the compound of formula (III)

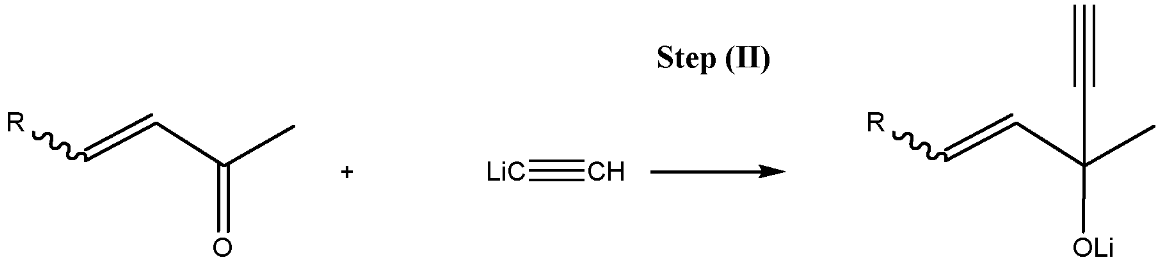


(III) ,

wherein

R has the same meanings as defined above,
is formed.

Reaction scheme of step (II):



R has the same meanings as defined above.

The compound of formula (II) is added to the reaction mixture until the Raman band approximately at 1885 cm^{-1} has disappeared. At this point, the addition of the compound of formula (II) is stopped (see Figure 6).

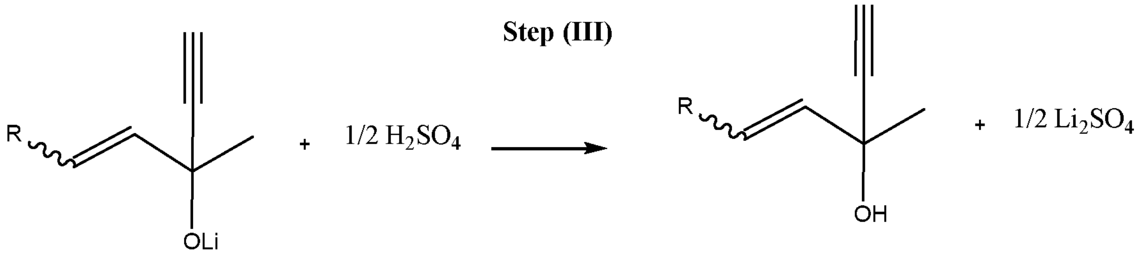
Raman spectroscopy indicates the point of total consumption of the lithium acetylide and the formation of the compound of formula (III) (band at approximately 2090 cm^{-1}).

Therefore, the present invention also relates to process (P5), which is process (P), (P'), (P''), (P'''), (P''''), (P1), (P2), (P3), (P3'), (P3'') or (P4), wherein the dosing of the compound of formula (II) is stopped when the band at approximately 1885 cm^{-1} has disappeared.

The temperature at step (II) is usually between -70°C and 0°C.

Therefore, the present invention also relates to process (P6), which is process (P), (P'), (P''), (P'''), (P''''), (P1), (P2), (P3), (P3'), (P3''), (P4) or (P5), wherein step (II) is carried out at a temperature between -70°C and 0°C.

The final step (step (III))



(III) **(I)**

,

wherein R has the same meanings as defined above,
is less critical in regard of producing unwanted side products, so therefore it is optional if this step is followed by Raman spectroscopy.

The step (III), which is the hydrolysis step, is usually carried out temperature of from -70°C and 0°C, preferably -40°C to -5°C.

Therefore, the present invention also relates to process (P7), which is process (P), (P’), (P”), (P”’), (P””), (P1), (P2), (P3), (P3’), (P3”), (P4), (P5) or (P6), wherein step (III) is carried out at a temperature between -70°C and 0°C.

Therefore, the present invention also relates to process (P7’), which is process (P), (P’), (P”), (P”’), (P””), (P1), (P2), (P3), (P3’), (P3”) (P4), (P5) or (P6), wherein step (III) is carried out at a temperature between -40°C to -5°C.

,

The hydrolysis in step (III) is carried out by using at least one Bronsted acid, such as: sulfuric acid, acetic acid, water, ammonium chloride.

Therefore, the present invention also relates to process (P8), which is process (P), (P’), (P”), (P”’), (P””), (P1), (P2), (P3), (P3’), (P3”), (P4), (P5), (P6), (P7) or (P7’), wherein step (III) the at least compound is chosen from the group consisting of sulfuric acid, acetic acid, water and ammonium chloride.

Therefore, the present invention also relates to process (P9), which is process (P), (P’), (P”), (P”’), (P””), (P1), (P2), (P3), (P3’), (P3”), (P4), (P5), (P6), (P7), (P7’) or (P8), wherein step (III) is carried out at a temperature between -70°C and 0°C.

Therefore, the present invention also relates to process (P9’), which is process (P), (P’), (P”), (P’”), (P””), (P1), (P2), (P3), (P3’), (P3”), (P4), (P5), (P6), (P7), (P7’) or (P8), wherein step (III) is carried out at a temperature between -40°C to -5°C.

At the end of step (III), the compound of formula (I) is obtained and isolated and purified by using commonly known methods.

Figure 1: Raman spectrum of ammonia
Figure 2: Raman spectrum of ammonia after addition of some of the lithium
Figure 3: Raman spectrum of acetylene solvated in ammonia
Figure 4: Raman spectrum of lithium carbide
Figure 5: Raman spectrum of lithium acetylide
Figure 6: Raman spectrum of the lithium alkoxide product III.
Figure 7: Raman spectra of the reactions Example 1 and Comparison Example 1 (C1)

The following examples illustrate the invention further without limiting it. All percentages and parts, which are given, are related to the weight and the temperatures are given in °C, and the pressures are absolute pressures when not otherwise stated.

EXAMPLES

Example 1

Ammonia gas is condensed into a cooled (-50 to -30 °C) 2L jacketed vessel fitted with a Raman probe under argon until the vessel contains approximately 500 ml of liquid ammonia. Lithium metal (10.5 g) is slowly added with stirring (Figure 1 -> Figure 2). Acetylene gas is added to the reaction mixture at a rate of approximately 1 L/min (Figure 3). The addition of acetylene is stopped when the Raman spectrum indicated formation of the lithium carbide (Figure 4).

The reaction temperature is increased to between -10 and +10 °C and diethyl ether (approximately 625 ml) is added. The reaction mixture is cooled to -15 to -5 °C and acetylene gas is added at a rate of approximately 1 L/min. When complete formation of the lithium acetylide is observed (Figure 5), a solution of methyl vinyl ketone (120 g in 120 ml of diethyl ether) is prepared and is added to the lithium acetylide solution at approximately 3.3 ml/min. The reaction is monitored by Raman spectroscopy and as soon as the consumption of the lithium acetylide is complete (Figure 6), the addition is stopped and the unused methyl vinyl ketone solution is disposed of (approx. 171 g of MVK solution added). The reaction mixture is stirred and then added over approximately 20 minutes to a cooled solution of sulfuric acid (30%, approximately 400 ml).

The ether layer is separated, dried over sodium sulfate and most of the ether is removed at normal pressure to give the crude 3-methylpent-1-en-4-yn-3-ol as a yellow oil (248.5g, 53.3 weight% content, 97.9% yield based on MVK and 91.3% yield based on lithium).

Comparative Example 1 (C1) (not using a Raman Spectroscopy to monitor the reaction progress)

The procedure of Example 1 was repeated, without the use of Raman spectroscopy using the same amounts of lithium metal and methyl vinyl ketone solution. The point at which the lithium acetylide was fully consumed was estimated to be reached after the addition of approximately 193g of the MVK solution (approx. 1.59 mol).

After work-up, 255.8g of crude 3-methylpent-1-en-4-yn-3-ol was obtained as a yellow oil (51.5 weight% content, 86.6% yield based on MVK). In addition, a polymer was formed (see Figure 7) that made the removal of the mixture from the reactor and purification significantly harder.

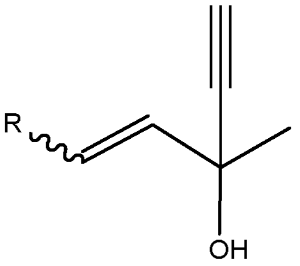
Comparative Example 2 (C2) (not using a Raman Spectroscopy to monitor the reaction progress)

The procedure of Example 1 was repeated, without the use of Raman spectroscopy using the same amounts of lithium metal and methyl vinyl ketone solution. The point at which the lithium acetylide was fully consumed was estimated to be reached after the addition of approximately 146g of the MVK solution (approx. 1.20 mol).

After work-up, 209.8g of crude 3-methylpent-1-en-4-yn-3-ol was obtained as a yellow oil (52.9 weight% content, 96.3% yield based on MVK and 76.5% yield based on lithium).

Claims

1. Process for the production of compounds of formula (I)



(I)

,

wherein

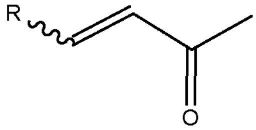
R is H; a linear, branched or cyclic C_1-C_{30} alkyl group, which can comprise ring systems and, which can be substituted with oxygen atoms; or a linear, branched or cyclic C_2 – C_{30} alkylene moiety, which can comprise ring systems and, which can be substituted with oxygen atoms, wherein

a first step lithium is added to NH_3 and then

ethyne (HCCH) is added to the reaction mixture and

in a second step (step (II))

a compound of formula (II)



(II)

,

wherein

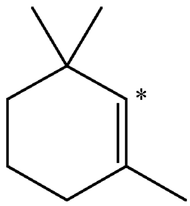
R and the wavy bond have the same meaning as defined for the compound of formula (I), and

then in a third step (step (III)) the obtained product is hydrolyzed,

characterized in that the steps (I) and step (II) and optionally step (III) are controlled by monitoring the reaction progress by using Raman spectroscopy.

2. Process according to claim 1, wherein R is H; a linear, branched or cyclic C_1-C_{15} alkyl group, which can comprise ring systems and, which can be substituted with oxygen atoms; or a linear, branched or cyclic C_1-C_{15} alkenyl group, which can comprise ring systems and, which can be substituted with oxygen atoms.

3. Process according to claim 1, wherein R is H; a linear or branched C_1-C_{10} alkyl group; a linear, branched or cyclic C_1-C_{15} alkenyl group, which comprise one carbon-carbon double bond; or a substituted cyclohexene ring chosen from the group consisting of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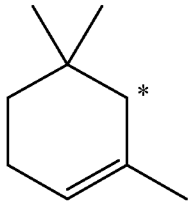
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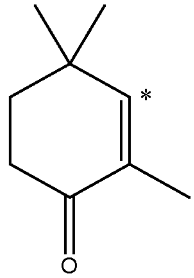
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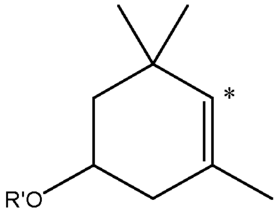
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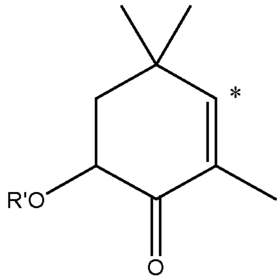
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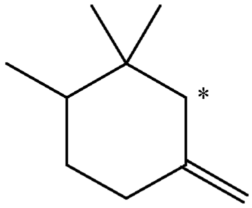
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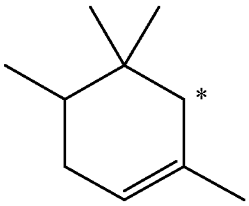
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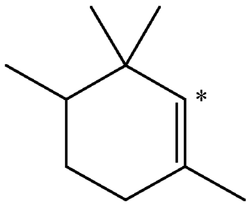
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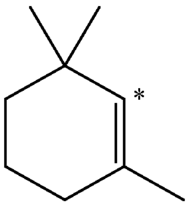
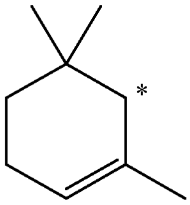
wherein the “*” shows the C bonding to the formula (I) and (II) and
R’ is H or a C_1-C_4 alkyl group or –(CO)C_1-C_4alkyl or -C(COCH$_3$)(CH$_3$)$_2$.

4. Process according to claim 1, wherein R is H; a linear or branched C_1-C_{10} alkyl group; a linear, branched or cyclic C_1-C_{15} alkenyl group, which comprise one carbon-carbon double bond; or a substituted cyclohexene ring chosen from the group consisting of


and

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wherein the “*” shows the C bonding to the formula (I) and (II).

5. Process according to claim 1, wherein R is H.

6. Process according to any of the preceding claims, wherein step (I) is carried out at a temperature range of from -90°C to -10 °C.

7. Process according to any of the preceding claims, wherein the dosing of acetylene is stopped when new peaks in the region of 1880-1835 cm^{-1} appear.

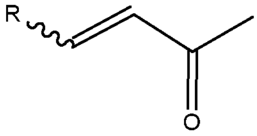
8. Process according to any of the preceding claims, wherein at least one inert solvent is added to the reaction mixture when two peaks in the region of 1880-1835 cm^{-1} are observed.

9. Process according to claim 8, wherein the at least one inert solvent is chosen from the group consisting of ethers and aromatic hydrocarbon compounds.

10. Process according to claim 8, wherein the at least one inert solvent is chosen from the group consisting of diethyl ether, di-n-propyl ether, diisopropyl ether, dioxane, tetrahydrofuran, 2-methyl tetrahydrofuran, benzene and toluene.

11. Process according to any of the preceding claims, wherein the dosing of acetylene is stopped when two peaks in the region of 1880-1835 cm^{-1} have disappeared and the peak approximately at 1885 cm^{-1} appears.

12. Process according to any of the preceding claims, wherein the dosing of the compound of formula (II)



(II) ,

wherein

R is H; a linear, branched or cyclic C_1-C_{30} alkyl group, which can comprise ring systems and, which can be substituted with oxygen atoms; or a linear, branched or cyclic C_2 – C_{30} alkylene moiety, which can comprise ring systems and, which can be substituted with oxygen atoms.is stopped when the band approximately at 1885 cm^{-1} has disappeared.

13. Process according to any of the preceding claims, wherein step (II) is carried out at a temperature between -70°C and 0°C.

14. Process according to any of the preceding claims, wherein step (III) is carried out at a temperature between -70°C and 0°C.

15. Process according to any of the preceding claims, wherein step (III) the at least compound is chosen from the group consisting of sulfuric acid, acetic acid, water and ammonium chloride.

Figures

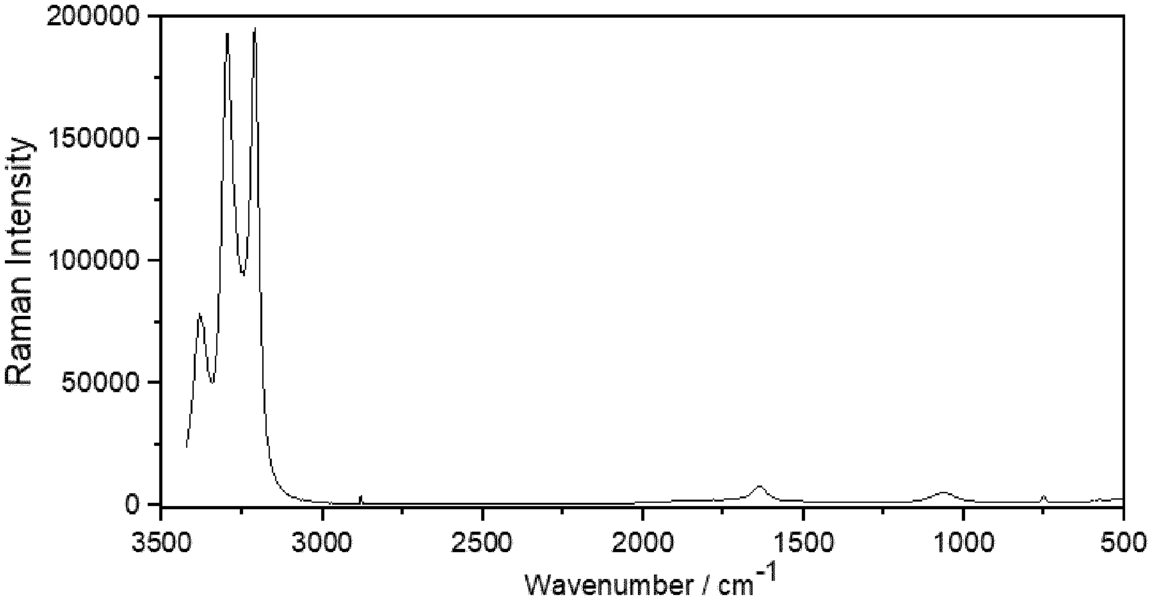


Figure 1: Raman spectrum of ammonia

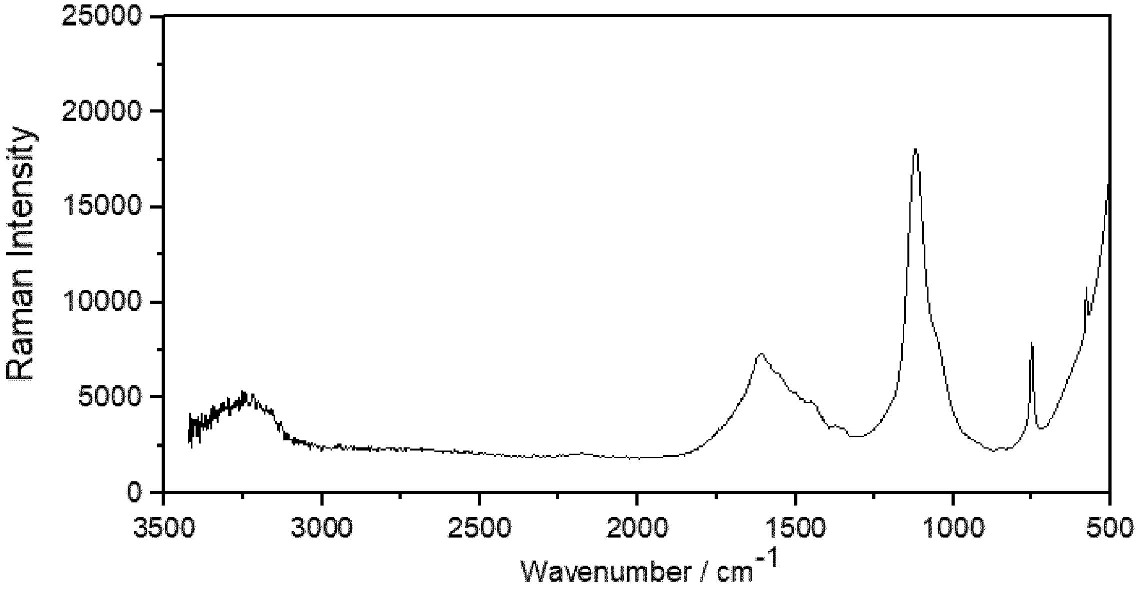


Figure 2: Raman spectrum of ammonia after addition of some of the lithium

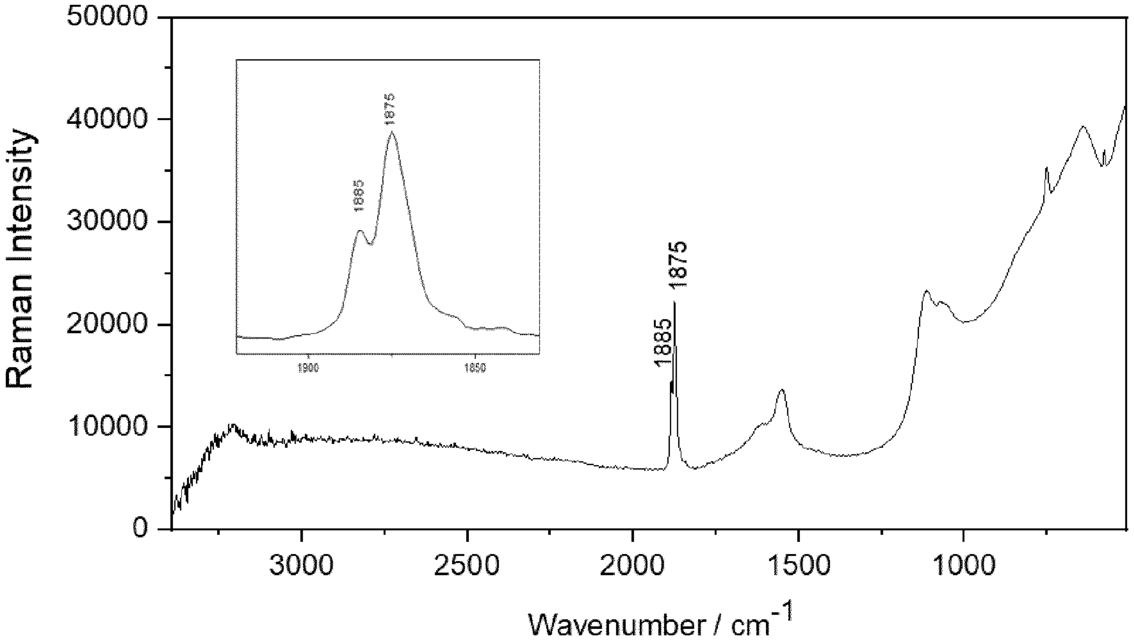


Figure 3: Raman spectrum of acetylene solvated in ammonia. Bands are visible in the 1895 – 1865 cm^{-1} region

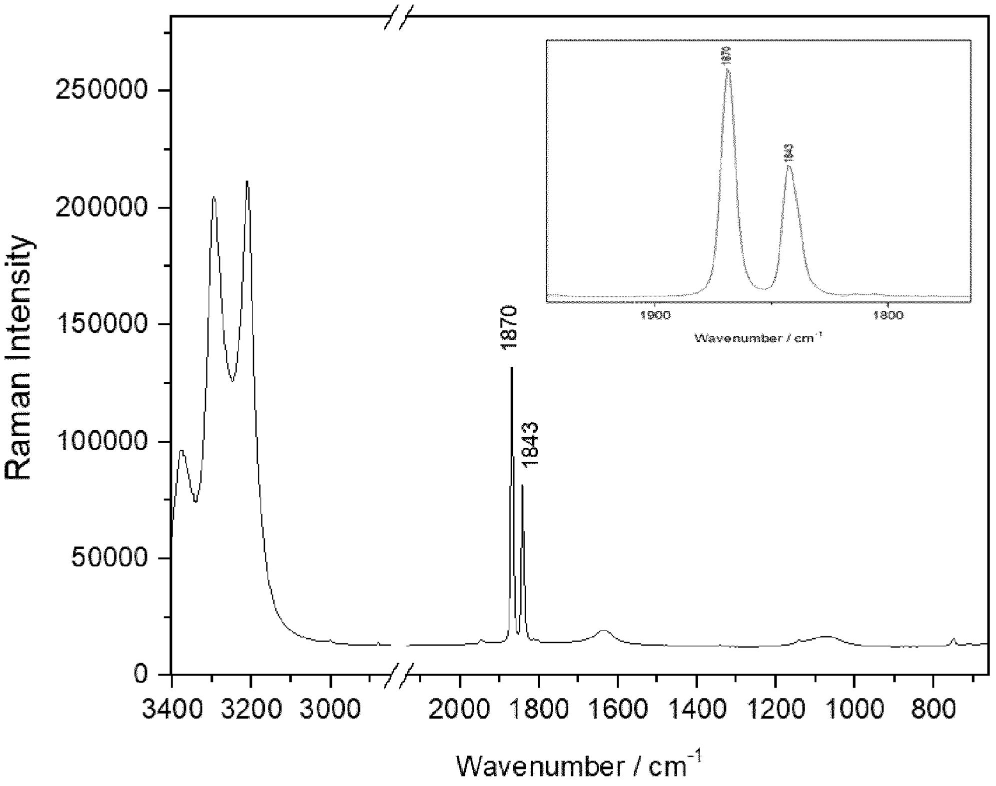


Figure 4: Raman spectrum of lithium carbide in ammonia. Bands are visible in the 1880 – 1835 cm^{-1} region.

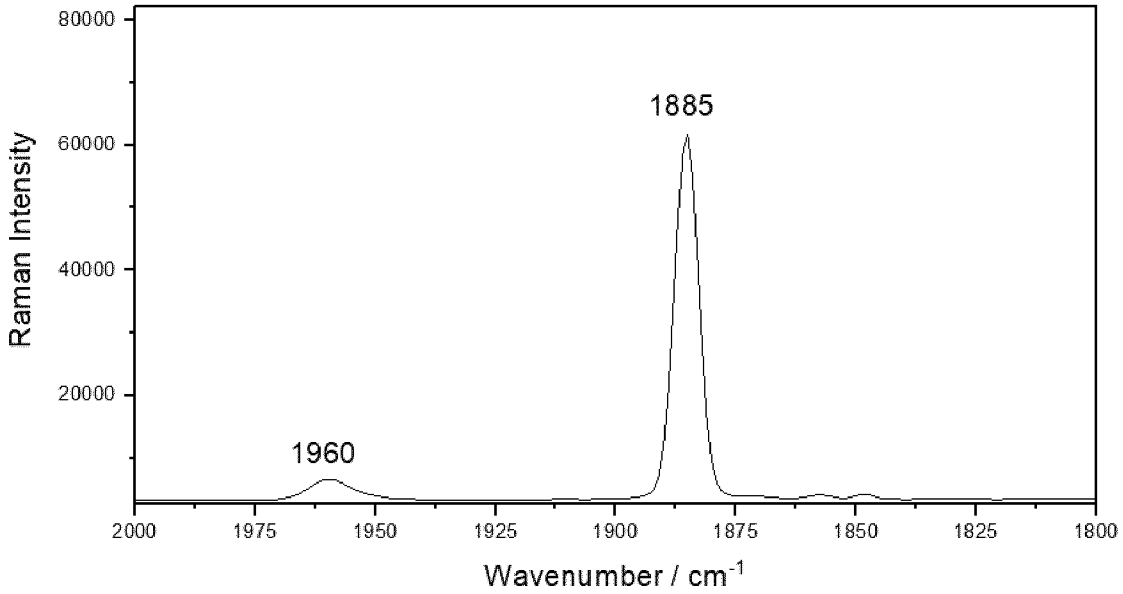


Figure 5: Raman spectrum of lithium acetylide.

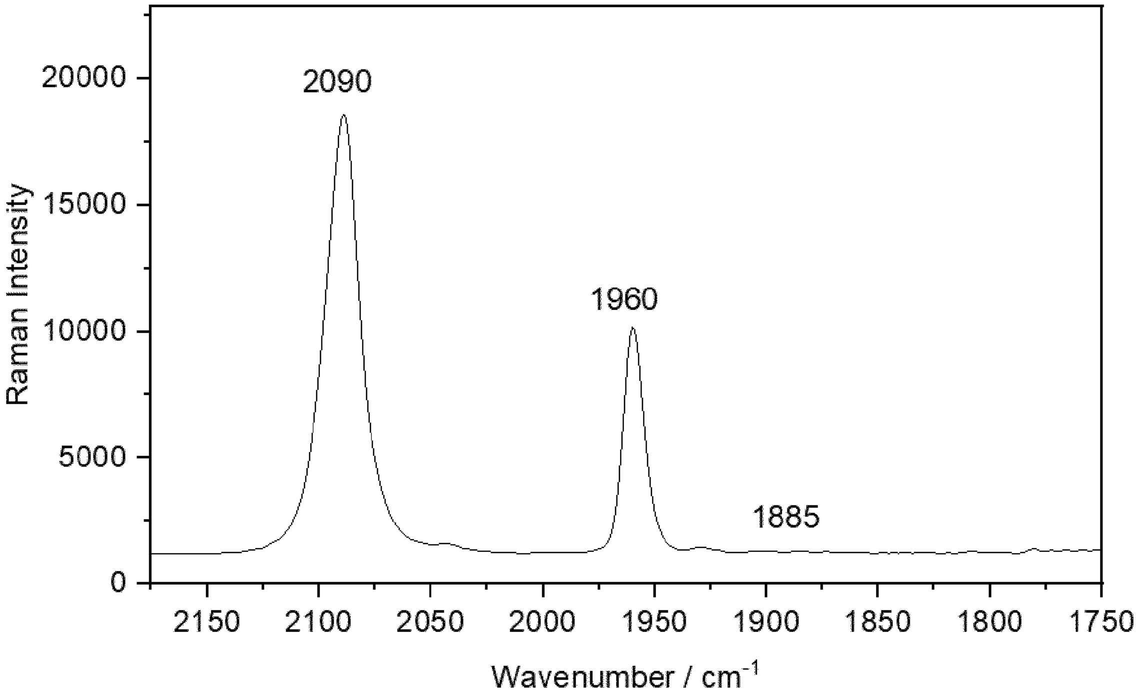


Figure 6: Raman spectrum of the lithium alkoxide product III.

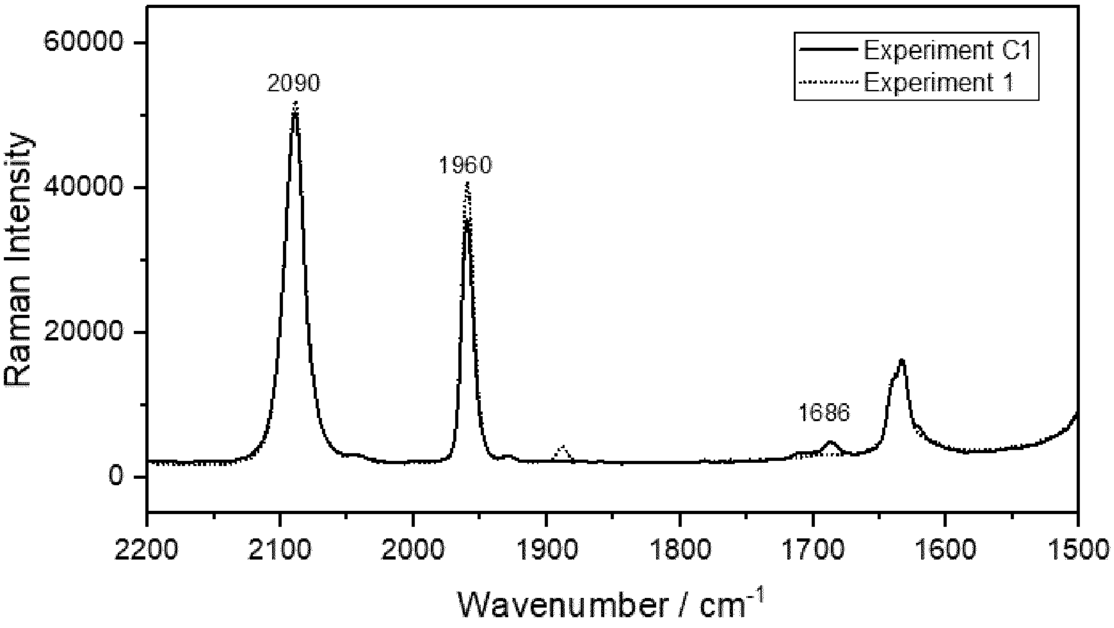


Figure 7: Raman spectra of the reactions Example 1 and C1. Example C1 contains polymer as indicated by the band at approximately 1685 cm^{-1}.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2022/086014

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C29/42 C07C33/048

ADD.

According to International Patent Classification (IPC) or to 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	K. R. Martin ET AL: "Ethynylation of Ketones Using Dilithium Acetylide", The Journal of Organic Chemistry, vol. 33, n°2, 1 February 1968 (1968-02-01), pages 778-780, XP055170759, DOI: 10.1021/jo01266a060 Retrieved from the Internet: URL:http://pubs.acs.org/doi/pdf/10.1021/jo01266a060 [retrieved on 2015-02-19] abstract page 779, table 1, beta-ionone, methyl vinyl ketone starting materials page 778, right-hand column, lines 9-19 ----- -/--	1-15

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 1 April 2023	Date of mailing of the international search report 12/04/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Fitz, Wolfgang

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2022/086014

C(Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014/078310 A1 (LYONDELL CHEMICAL TECH LP [US]; WHITE DANIEL F [US] ET AL.) 22 May 2014 (2014-05-22) paragraphs [0006] - [0007] -----	1-15
A	US 4 320 236 A (WIEDERKEHR HERMANN) 16 March 1982 (1982-03-16) cited in the application the whole document -----	1-15

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2022/086014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014078310 A1	22-05-2014	CN 104768909 A	08-07-2015
		EP 2920137 A1	23-09-2015
		TW 201429934 A	01-08-2014
		US 2014135537 A1	15-05-2014
		WO 2014078310 A1	22-05-2014
US 4320236 A	16-03-1982	CH 642936 A5	15-05-1984
		US 4320236 A	16-03-1982