

Description

Method for producing a radioactively labeled carboxylate

The present invention relates to the technical field of radioactively labeled carbon compounds. In particular, the present invention relates to a method for producing a radioactively labeled carboxylate and to the use of radioactively labeled carbon dioxide and a microelectrode for the electrochemical synthesis of radioactively labeled carboxylate.

Positron emission tomography (PET) is a method in nuclear medicine which produces sectional images of living organisms. During PET, the distribution of a radioactively labeled substance, a radiopharmakon, in the organism is shown, by means of which the structure and also biochemical and physiological processes are illustrated. A radiopharmakon is labeled by a radionuclide, a radioactive atom or isotope.

In contrast to conventional scintigraphy, PET uses radioactively labeled substances which give off positron radiation. In the event of interaction of a positron with an electron in the body, two high-energy photons are emitted in opposite directions. The principle of PET consists in recording these coinciding photons by means of detectors which face one another. The distribution in respect of time and space of these registered decay events is used to deduce the spatial distribution of the radiopharmakon in the body.

A frequent application of PET is in metabolic diseases, particularly in oncology, neurology and cardiology. The radiopharmakon is enriched by many aggressive tumors, meaning that PET is suitable e.g. for the diagnosis, stage determination and progression monitoring of cancer diseases. Similarly, PET can be used to illustrate the circulation and thus the metabolic activity of neuronal and cardiac tissue. Similarly, PET can be used to detect chronically poorly vascularized areas within the heart muscle.

The organism does not differentiate between radiopharmakons and the corresponding non-radioactive compounds, meaning that radiopharmakons are metabolized normally. On account of the decay of the radionuclide, the radiopharmakon can be traced and visualized.

The radionuclides used most often are radioactive isotopes of the elements carbon (^{11}C), fluorine (^{18}F), nitrogen (^{13}N) and oxygen (^{15}O). These radionuclides are produced in a cyclotron by particle acceleration.

The usefulness of radiopharmakons is limited by the short half-life of the radionuclides of typically less than 2 hours. The radionuclide ^{11}C has a particularly short half-life at only ca. 20 minutes. The undesired decay in radioactivity starts as early as during the production of the radionuclide in the cyclotron and continues during the production of the radiopharmakon, its delivery to the PET site and finally to the point of administration to the patients and measurement.

In order to achieve the widest possible supply radius in which the positron emission tomograph to be supplied is

located around the cyclotron, the highest possible radioactivity of the radiopharmakon after its production must be present. This can be achieved by the shortest possible production time of the radiopharmakon from the radionuclide since the decay of the radioactivity of a radionuclide depends on the time.

The basis for producing a radiopharmakon is a molecule that is biochemically or physiologically active in the organism and in whose chemical structure one or more radionuclides are incorporated. Conventional methods utilize the route via the methylating agent $^{11}\text{CH}_3\text{I}$, in order, for example, to radioactively label amines or carboxylic acids with ^{11}C (Denutte et al., 1983; Vandersteene and Slegers, 1996). However, in this process, the $^{11}\text{CO}_2$ produced in the cyclotron has to be further reacted in a two-stage process with LiAlH_4 and HI to give $^{11}\text{CH}_3\text{I}$. Only in a third step can the radioactively labeled methylating agent be transferred to the pharmakon to be labeled. As a result of this laborious synthesis of the radiopharmakon, a high proportion of the radioactivity originally provided by the $^{11}\text{CO}_2$ is lost.

Important technology has been introduced for new PET contrast agents in the field of ^{18}F labeling by means of so-called "click chemistry". This method permits the synthesis of radioactive contrast agents in a single step (Devaraj et al., 2009; Li et al., 2007). Radiopharmakons labeled with fluorine, e.g. ^{18}F -fluorouracil, ^{18}F -6-fluoro-DOPA or ^{18}F -fluoro-2-deoxy-D-glucose, however, differ from their corresponding non-labeled origin molecules, and so it is desired to use hydrocarbon compounds which do not differ chemically from their origin molecules.

It was therefore the object of the present invention to provide an efficient method by which a radioactively labeled hydrocarbon compound can be synthesized within a short production time with high yield.

This object is achieved by a method for producing a radioactively labeled carboxylate which involves the steps:

- provision of at least one precursor molecule of the carboxylate in a solvent which comprises a conductive salt;
- introduction of at least one reactant which comprises radioactively labeled carbon dioxide into the solvent; and
- electrochemical reaction of the precursor molecule with the radioactively labeled carbon dioxide to give the radioactively labeled carboxylate;

where the radioactively labeled carbon dioxide during the reaction of the precursor molecule is completely dissolved in the solvent.

In addition, the present invention relates to the use of radioactively labeled carbon dioxide for the electrochemical synthesis of a radioactively labeled carboxylate, where the carbon dioxide during the synthesis is completely dissolved in a solvent.

In addition, the present invention relates to the use of a microelectrode for the electrochemical synthesis of a radioactively labeled carboxylate, where radioactively labeled carbon dioxide is reacted.

The dependent claims contain advantageous embodiments of the invention.

The present invention is described in more detail below by reference to the attached figures.

Figure 1 shows an electrochemical reductive carboxylation of a ketone with incorporation of $^{11}\text{CO}_2$ for the synthesis of a radioactively labeled alpha- ^{11}C -amino acid.

Figure 2 shows an electrochemical reductive carboxylation of a ketone with incorporation of $^{11}\text{CO}_2$ for the synthesis of a radioactively labeled alpha- ^{11}C -hydroxy acid.

Figure 3 shows a reductive carboxylation for producing an amino acid by reacting an imine with a radioactively labeled cyanide.

Figure 4 shows two microelectrodes, cathode 1 and anode 3, and also their arrangement relative to one another.

The present invention provides a method for producing a radioactively labeled carboxylate which involves the steps:

- provision of at least one precursor molecule of the carboxylate in a solvent which comprises a conductive salt;
- introduction of at least one reactant which comprises radioactively labeled carbon dioxide into the solvent; and
- electrochemical reaction of the precursor molecule with the radioactively labeled carbon dioxide to give the radioactively labeled carboxylate;

where the radioactively labeled carbon dioxide during the reaction of the precursor molecule is completely dissolved in the solvent.

The term "carboxylate", as used here, refers to a compound which includes a carboxyl group, e.g. of the empirical formula $R_1R_2R_3C(COO^-)$. The radicals R_1 , R_2 , R_3 bonded to the central carbon atom can be identical or different saturated or unsaturated linear, branched or cyclic aliphatic, aromatic or heteroaromatic radicals or mixed forms thereof. It is a prerequisite that the radicals do not contain groups which are themselves reactive under the carboxylation conditions according to the invention. The carboxylate includes in particular carboxylate amides, imides, anhydrides, carboxylic esters, carboxylic halides, aldehydes, ketones, amino acid salts, hydroxy acid salts, urethanes and carboxylic acid.

The term "precursor molecules", as used here, refers to starting substances and starting compounds of the carboxylate synthesis, such as e.g. imines or carbonyl compounds (cf. figs 1 to 3).

The term "conductive salt", as used here, refers to an electrolyte dissolved in the solvent which conveys current.

The term "reactants", as used here, includes chemical molecules, such as carbon dioxide, cyanide, water and ammonia, and also protons and electrons. The introduction of the reactants into the solvent can take place in one or more steps, meaning that the reactants can be introduced simultaneously, with an overlap or in succession.

The term "electrochemically", as used here, refers to a chemical reaction by means of electrolysis.

The term "dissolved carbon dioxide" refers to both physically dissolved carbon dioxide and also to hydrogen carbonate. The term "completely dissolved", as used here, means that no gas phase arises in the solvent. The term likewise refers to the complete saturation of the solvent with carbon dioxide. The complete dissolution can take place by predissolving the carbon dioxide prior to the start of the reaction under very high pressure in the solvent.

In the method according to the invention for producing a radioactively labeled carboxylate, short reaction times and therefore production times, and also a high yield of the carboxylate, are achieved by dissolving the radioactively labeled carbon dioxide completely.

As a result of completely dissolving the carbon dioxide, its concentration in the solvent is increased. Concentration gradients due to an undissolved gas phase are avoided. The complete dissolution of the carbon dioxide leads to a better mixing and a homogeneous concentration of the carbon dioxide in the solvent. Overall, therefore, the reaction time and production time are shortened and the yield is increased.

As a result of the short reaction time and production time, radiochemical yield losses due to the natural decay of the radionuclide as a function of time are in turn reduced.

The rapid radioactive decay of radioactive ^{11}C hitherto made it necessary for an extremely high dose of radioactive starting substances to be used for the synthesis of the carboxylate radiopharmakon. By shortening the reaction time by means of the method according to the invention, the dose of radioactive carbon which

is used during the carboxylate synthesis can be reduced. This saves costs, and the radioactive burden of the radiochemist during the production of the radioactively labeled carboxylate is reduced.

The reaction according to the invention of the precursor molecule with the radioactively labeled carbon dioxide is very simple and can be carried out with low expenditure on apparatus. Intermediates do not have to be isolated or purified. The method according to the invention can therefore be used directly in the clinic or the radiological surgery.

The reaction according to the invention of the precursor molecule with radioactively labeled carbon dioxide takes place by means of a reductive electrochemical carboxylation via a short and rapid synthesis route. The radioactively labeled carbon dioxide is incorporated into the precursor molecule during the last step of the carboxylate synthesis according to the invention, i.e. only one synthesis step before the carboxylate end product (cf. fig. 1 and 2). The carboxylation and also the labeling take place in a single step, which is not followed by any other synthesis steps.

A carboxylate synthesis with carbon dioxide is described in EP 0 189 120 A1, although no radioactively labeled carbon dioxide is used therein. Similarly, no completely dissolved carbon dioxide, but gaseous carbon dioxide, is used, meaning that in EP 0 189 120 A1 the yield is lower and the reaction time is longer. Since EP 0 189 120 A1 does not relate to the production of radioactively labeled carboxylate, these disadvantages are less serious since non-radioactive carboxylate does not decay as a function of time, but is stable. Moreover, the amount of starting substances used in EP 0 189 120 A1 is not a critical factor because no radioactive burden occurs.

In a preferred embodiment, the carboxylate is an alpha-hydroxy acid salt and/or an alpha-amino acid salt. The prefix "alpha-" refers to the position of the carboxyl group on the alpha-carbon atom to which the hydroxyl group or amino group is also attached.

The alpha-hydroxy acid salt is synthesized in a single-stage reaction directly from a ketone or an aldehyde, with incorporation of the radioactively labeled carbon dioxide (figure 1). It is therefore a very rapid and simple reaction with low radiochemical yield losses due to natural decay. It is therefore possible to reduce the dose of the radioactive carbon dioxide used and thus to reduce the radioactive burden.

The precursor molecule for producing the alpha-amino acid salt is synthesized by means of the first part of the established Strecker reaction (figures 1 and 3). Alpha-amino acid salts can be synthesized by the method according to the invention with a higher yield than alpha-hydroxy acid salts. Alpha-amino acid salts, just like alpha-hydroxy acid salts and acids thereof, are physiologically important molecules that are widespread in the metabolism, meaning that they are customary PET biomarkers with diverse use.

In a further embodiment, the precursor molecule comprises ketimine, aldimine, ketone, aldehyde and/or ions thereof. Aldimine has the formula R_1HCNR_2 , ketimine the formula $R_1R_2CNR_3$, ketone the formula R_1R_2CO and aldehyde the formula R_1HCO . One example of a ketimine ion is an iminium cation (fig. 3). The radicals R_1 , R_2 and R_3 can either be identical or different aromatic, heteroaromatic and aliphatic radicals. The aliphatic radicals include acyclic

branched and unbranched, cyclic and alicyclic, saturated and unsaturated carbon compounds. It is a prerequisite that the radicals do not contain groups which are themselves reactive under the carboxylation conditions. These precursor molecules are cost-effective, commercially available and simple to produce using standard methods.

In a preferred embodiment, the conductive salt comprises alkali metal halide, alkaline earth metal halide, ammonium halide, alkyl, cycloalkyl, arylammonium salt or quaternary ammonium salts, in particular tetra(C₁-C₄)alkylammonium tetrafluoroborate or tetra(C₁-C₄)alkylammonium hexafluorophosphate. The radicals bonded to the nitrogen of the quaternary ammonium salt are identical or different aliphatic, cycloaliphatic or aromatic radicals. Chloride, bromide, iodide, tetrafluoroborate, hexafluorophosphate, para-toluenesulfonate, perchlorate and bis(trifluoromethylsulfonimide) are preferred anions of the quaternary ammonium salts. Tetra(C₁-C₄)alkylammonium tetrafluoroborate or hexafluorophosphate are preferred conductive salts, such as e.g. tetrabutylammonium tetrafluoroborate.

In a further embodiment, the solvent is an organic solvent. Preferred solvents are amide, nitrile, N,N-dimethylformamide (DMF) and/or an open-chain or cyclic ether.

In a further embodiment, the reactant reacts with the precursor molecule in one step to give the carboxylate. Consequently, the reaction time is short and the radioactive yield losses over the period are low.

In a further embodiment, the radioactively labeled carbon dioxide is ¹¹CO₂.

In a further embodiment, the carbon dioxide is introduced into the solvent under a pressure of more than 2 bar, preferably 5 bar or more than 5 bar. As a result of this high pressure, the carbon dioxide during the reaction of the precursor molecule is dissolved completely in the solvent.

In a further preferred embodiment, the reaction takes place in a continuous-flow reactor. The continuous-flow reactor is operated in a continuous procedure, as a result of which the reaction equilibrium is shifted in the synthesis direction. This leads to a high yield, to a high selectivity and also to a low concentration of undesired by-products.

In a further embodiment, the reaction takes place on a microstructure. The term "microstructure", as used here, refers to miniaturized units and systems both in the micrometer and also in the nanometer range, such as e.g. microcontainers, micromixers, microelectrodes and microstirrers.

The use of the microstructure ensures an improved surface/volume ratio of the reaction space. The improved surface/volume ratio leads to a rapid mixing, an effective heat and current transfer and short controllable residence times of the solvent and also of the substances present therein. Methods using microstructures can therefore be operated more efficiently and lead to short reaction times and high yields.

The very good controllability of the syntheses on microstructures and the small amount of health-endangering solvents and also the toxic reactants present therein and

in particular the radiopharmakons lead to high operational safety. The microstructure used in the course of the invention therefore reduces the radiation burden and also the burden due to health-endangering substances to the radiochemist during the synthesis of the radioactively labeled carboxylate.

During the method according to the invention for producing a radioactively labeled carboxylate, short reaction times and therefore production times and also a high yield of the carboxylate are achieved by the carboxylation taking place on a microstructure. As a result of the short reaction and production time, radiochemical yield losses due to natural decay of the carbon radionuclide as a function of the time are reduced. The amount of carbon radionuclide used in the synthesis of the radioactively labeled carboxylate can therefore be reduced, as a result of which costs are saved and the burden to the radiochemist during the synthesis is reduced.

In a further embodiment, the microstructure includes at least one microelectrode.

During the carboxylation with carbon dioxide, the reduction can take place electrochemically with the help of microelectrodes. In this process, a sacrificial anode serves as electron donor, meaning that the use of toxic cyanide or hydrogen cyanide as electron donor can be dispensed with. As a result of the electrochemical catalysis, the method can be operated with high yield and high selectivity. Readily accessible compounds, such as aldehydes or ketones, serve as precursors.

The microelectrode comprises a microanode or microcathode. Anode materials are soluble metals, in particular

aluminum, magnesium, zinc, copper or alloys thereof, with aluminum and magnesium being most preferred. Preferred cathode materials are conductive materials, such as conductive carbon materials, e.g. graphite, carbon fiber web and glassy carbon, and also nickel and magnesium, with magnesium being most preferred. Particularly preferred combinations of anode and cathode are magnesium-magnesium and magnesium-carbon combinations.

On account of their geometry, the microelectrodes can be arranged close to one another. As a result of the spatial proximity, the field strength increases for the same voltage, meaning that it is possible to work with lower voltages for the same field strength.

The potential difference between the microelectrodes depends on the reacted molecules and is ascertained experimentally by analytical methods. The electrolysis can be operated between the microelectrodes galvanostatically, although a potentiostatic procedure is preferred on account of the small amounts and volumes of solvent, conductive salt, reactant and precursor molecule.

In a further embodiment, the microstructure comprises two microelectrodes which are located in an undivided space. The undivided electrode space has the advantage that the product selectivity is increased as a result of the salt formation with the cation of the dissolving sacrificial anode. The salt formation protects against undesired secondary reactions, e.g. a reduction of the precursor molecules to give pinacol derivatives. Moreover, in undivided spaces, no ohmic resistance is built up as a result of a separation membrane.

In a further preferred embodiment, the microelectrode comprises a coating, a tubular module, e.g. a microcapillary, a linear element, e.g. a wire, a two-dimensional lattice, a two-dimensional surface or a three-dimensional mesh. As a result of these electrode variants, the surface/volume ratio is further improved.

In a particularly preferred embodiment, the tubular module is a cathode 1 and the linear element is an anode 3. The anode 3 is arranged centrally inside the cathode 1. The cathode 1 and the anode 3 are arranged relative to one another such that the longitudinal direction of the cathode 1 and the longitudinal direction of the anode 3 run parallel to one another (figure 4).

In a particularly preferred embodiment, the two-dimensional surface is in each case an anode and a cathode which are arranged on the opposite walls of a rectangular microstructure. An arrangement of a two-dimensional anode and cathode on the opposite walls of a flat rectangular microstructure advantageously combines a homogeneous field in the electrode space with favorable flow ratios of the reactants, as a result of which the electrochemical reaction is configured more efficiently and the reaction time is reduced. Moreover, the yield is increased with simultaneous minimization of the secondary reactions due to a homogeneous residence time in this microstructure.

In a particularly preferred embodiment, the reaction temperature is 20°C to 30°C. In a further embodiment, the concentration of the precursor molecule in the solvent is 0.1 M.

In a further embodiment, the method further involves the step of the acidic hydrolyzation of at least one carboxyl group of the carboxylate. As a result of the acidic hydrolysis, e.g. by means of hydrochloric acid, from the carboxylate, with the addition of a proton, the corresponding carboxylic acid is obtained, from the amino acid salt the corresponding amino acid is obtained and from the hydroxy acid salt the corresponding hydroxy acid is obtained.

Furthermore, the method according to the invention involves the step of isolation of the carboxylic acid from the solvent. The isolation preferably takes place by precipitation, filtration, evaporation, preparative chromatography and/or decantation and likewise involves the separation off from the conductive salt and desired and undesired by-products. The precipitation takes place for example by means of a low-polarity solvent. In a further step, the acid function of the carboxylic acid can be derivatized, e.g. with methanol and sulfuric acid. In a further step, the carboxylic acid can also be analyzed, e.g. by chromatography, in particular by gas chromatography.

In addition, the present invention relates to a method for producing a radioactively labeled carboxylate, involving the steps:

- provision of at least one precursor molecule in a solvent;
- addition of at least one reactant which comprises radioactively labeled cyanide to the solvent; and
- reaction of the precursor molecule with the reactant to give the radioactively labeled carboxylate,

where the reaction takes place on a microstructure.

Figure 3 shows by way of example the reductive carboxylation using cyanide.

In addition, the present invention relates to the use of radioactively labeled carbon dioxide for the electrochemical synthesis of a radioactively labeled carboxylate, where the carbon dioxide during the synthesis is completely dissolved in a solvent.

In addition, the present invention relates to the use of a microelectrode for the electrochemical synthesis of a radioactively labeled carboxylate, where radioactively labeled carbon dioxide is reacted.

The above variants and embodiments in respect of the first subject matter of the invention also relate to the other subjects of the invention.

The formula schemes in figures 1 to 4 show selected examples of the carboxylation according to the invention.

Figure 1 shows the synthesis of an alpha-amino acid by means of reductive electrochemical carboxylation. The precursor molecule, an iminium cation of the formula $(R_1R_2C(NH_2))^+$, is synthesized for example by means of the Strecker synthesis from a ketone, R_1R_2O , with ammonia and hydrogen with the elimination of water. The iminium cation is reduced by absorbing two electrons and, by adding radioactively labeled carbon dioxide, is reacted to give an amino acid salt, $R_1R_2(H_2N)^{11}C(COO^-)$, as a result of which the carbon atom of the carboxyl group becomes radioactively labeled. The carboxyl group is further hydrolyzed with the addition of a proton, meaning that the amino acid salt is reacted to give the amino acid. In the case of this synthesis, it is possible to dispense with protecting the acidic protons.

Figure 2 shows the synthesis of an alpha-hydroxy acid by means of reductive electrochemical carboxylation. The precursor molecule is a ketone, R_1R_2CO , which is reduced by absorbing two electrons and, by adding radioactively labeled carbon dioxide, is reacted to give an alpha-hydroxy acid salt, $R_1R_2HO^{11}C(COO^-)$. The alpha-hydroxy acid salt is hydrolyzed to the alpha-hydroxy acid by adding a proton.

Figure 3 shows the synthesis of a radioactively labeled nitrile from an imine with the incorporation of a proton and also radioactively labeled cyanide, $^{11}CN^-$. The radioactively labeled nitrile can be hydrolyzed further to give an amino acid.

Figure 4 shows an embodiment of an electrochemical micro continuous-flow reactor which has a capillary tube, the inside tube wall of which constitutes the cathode 1. Furthermore, the micro continuous-flow reactor has a wire, the anode 3, located centrally in the capillary tube.

Literature citations

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Abstract for Devaraj et al., Bioconjugate Chem 20(2), 397-401, 2009

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EP 0 189 120 A1

Claims

1. A method for producing a radioactively labeled carboxylate, involving the steps:
 - provision of at least one precursor molecule of the carboxylate in a solvent which comprises a conductive salt;
 - introduction of at least one reactant which comprises radioactively labeled carbon dioxide into the solvent; and
 - electrochemical reaction of the precursor molecule with the radioactively labeled carbon dioxide to give the radioactively labeled carboxylate;characterized in that the radioactively labeled carbon dioxide during the reaction of the precursor molecule is completely dissolved in the solvent.
2. The method as claimed in claim 1, characterized in that the carboxylate is an alpha-hydroxy acid salt and/or an alpha-amino acid salt.
3. The method as claimed in claim 1 or 2, characterized in that the precursor molecule is selected from the group consisting of ketimine, aldimine, ketone, aldehyde and ions thereof.
4. The method as claimed in one of the preceding claims, characterized in that the conductive salt is selected from the group consisting of alkali metal halide, alkaline earth metal halide, ammonium halide, alkyl-, cycloalkyl-, arylammonium salt

and quaternary ammonium salts, in particular tetra(C₁-C₄)alkylammonium tetrafluoroborate and tetra(C₁-C₄)alkylammonium hexafluorophosphate.

5. The method as claimed in one of the preceding claims, characterized in that
the solvent is an organic solvent, in particular selected from the group consisting of amide, nitrile, N,N-dimethylformamide and open-chain and also cyclic ether.
6. The method as claimed in one of the preceding claims, characterized in that
the reactant is reacted with the precursor molecule in one step to give the carboxylate.
7. The method as claimed in one of the preceding claims, characterized in that
the radioactively labeled carbon dioxide is ¹¹CO₂.
8. The method as claimed in one of the preceding claims, characterized in that
the carbon dioxide is introduced into the solvent under a pressure of more than 2 bar, preferably 5 bar or more than 5 bar.
9. The method as claimed in one of the preceding claims, characterized in that
the reaction takes place in a continuous-flow reactor.
10. The method as claimed in one of the preceding claims, characterized in that
the reaction takes place on a microstructure.

11. The method as claimed in claim 10,
characterized in that
the microstructure comprises at least one microelectrode.
12. The method as claimed in claim 10 or 11,
characterized in that
the microstructure comprises two microelectrodes which are
located in an undivided space.
13. The method as claimed in one of claims 10 to 12,
characterized in that
the microstructure is selected from the group consisting
of a coating, a tubular module, a linear element, a two-
dimensional lattice, a two-dimensional surface and a
three-dimensional mesh.
14. The method as claimed in claim 13,
characterized in that
the tubular module is a cathode (1) and the linear element
is an anode (3) which is arranged centrally inside the
cathode (1), and the cathode (1) and the anode (3) are
arranged relative to one another such that the
longitudinal direction of the cathode (1) and the
longitudinal direction of the anode (3) run parallel to
one another.
15. The method as claimed in claim 13,
characterized in that
the two-dimensional surface is in each case an anode and a
cathode which are arranged on the opposite walls of a
rectangular microstructure.

16. The method as claimed in one of the preceding claims, further involving the step:
 - acidic hydrolyzation of at least one carboxyl group of the carboxylate.
17. The method as claimed in one of the preceding claims, further involving the step:
 - isolation of the carboxylic acid from the solvent.
18. The use of radioactively labeled carbon dioxide for the electrochemical synthesis of a radioactively labeled carboxylate, characterized in that the carbon dioxide during the synthesis is completely dissolved in a solvent.
19. The use of a microelectrode for the electrochemical synthesis of a radioactively labeled carboxylate, characterized in that radioactively labeled carbon dioxide is reacted.