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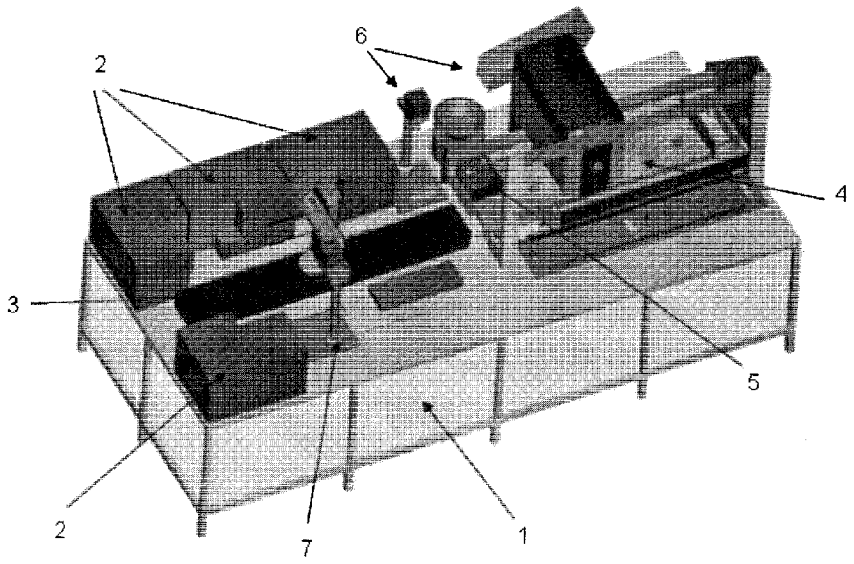
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) **Title:** AUTOMATED DEVICE COMPRISING MICROWAVE IRRADIATION FOR SYNTHESIS OF ORGANIC COMPOUND LIBRARIES



(57) **Abstract:** The present invention relates to a device for fully automated synthesis of a plurality of different organic compounds. The device comprises at least the following functional units: a) storage systems for a plurality of reaction vials and stock solutions, b) a transport system with a robotic arm capable of carrying a single reaction vial to the various functional units of the device, c) pipetting station including a transfer station for the preparation of reaction mixtures in the reaction vials from stock solutions and reagents solutions, d) one or more microwave instrument for heating the reaction mixture under appropriate pressure and temperature under microwave irradiation for the synthesis reaction, e) computer-based means for controlling the system for complete autonomy during the process, and f) a capping station for sealing the reaction tubes.

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AUTOMATED DEVICE COMPRISING MICROWAVE IRRADIATION FOR SYNTHESIS OF ORGANIC COMPOUND LIBRARIES

The present invention relates to a device for the fully automated synthesis of a plurality of different organic compounds. The device comprises at least the following functional units:

- storage systems for a plurality of reaction vials and stock solutions,

- a transport system with a robotic arm capable of carrying a single reaction vial to the various functional units of the device,

- a pipetting station including a transfer station for the preparation of reaction mixtures in the reaction vials from stock solutions and reagents solutions,

- one or more microwave instrument for heating the reaction mixture under appropriate pressure and temperature under microwave irradiation for the synthesis reaction,

- computer-based means for controlling the system for complete autonomy during the process,

- a capping station for sealing the reaction tubes.

The generation of chemical libraries, also referred to as chemical compound libraries, or small molecule libraries, is necessary for screening against a rapidly growing range of therapeutic targets resulting from genomics research. In the post-genomic era, the explosion of new therapeutic targets has also prompted chemists to discover innovative compounds for new targets as effectively and efficiently as possible.

Due to robotisation and miniaturization, the task of biological screening of small molecules has made tremendous progress during the last decade. The number of compounds that can be screened daily has increased from tens to thousands and the availability of a large number of compounds to feed the screening robots has become a major rate limiting step. Tools such as combinatorial chemistry and parallel synthesis have been developed to allow the rapid generation of large compound libraries.

Innovative compounds can be synthesized by the use of microwave heating in a process now known as microwave-assisted organic synthesis (MAOS). Direct microwave heating at

temperature as high as 250°C and under pressure as high as 20 bars is not only able to reduce reaction chemical reaction times from hours to minutes, but it is also known to increase yields, to reduce side reactions, to reduce costs as less starting materials are needed, to improve reproducibility and to discover novel reaction pathways. This monumental achievement, which contributes to the expansion of the chemical as well as the medicinal chemistry space, has become a really established technique and has been applied with great success for a couple of years in chemistry labs on a low throughput level.

However, to the best of Applicant's knowledge, the highest capacity for commercially available systems is 240 vials with liquid handling. Therefore, there is a need for improving instruments and associated methods for enabling the synthesis of a high-number of compounds in a reduced amount of time (high-throughput).

The present invention provides a device capable of carrying out in one run, in a fully automated manner, more than 4000 different chemical reactions with reduced reaction times. The device of the invention can rapidly carry out, in an unattended and independent fashion, up to approximately 2000 chemical reactions in 60 hours.

As used herein, by "carrying out chemical reactions", it is meant that the execution of these chemical reactions enables the preparation of compounds with different chemical structures, wherein such structures are predefined before starting the process by the user of the device.

In a first embodiment, the invention is a device for the fully automated synthesis of a plurality of different organic compounds, comprising at least the following functional units:
- storage systems for a plurality of reaction vials and stock solutions,
- a transport system with a robotic arm capable of carrying a single reaction vial to the various functional units of the device,
- a pipetting station including a transfer station for the preparation of reaction mixtures in the reaction vials from stock solutions and reagents solutions,
- one or more microwave instrument for heating the reaction mixture under appropriate pressure and temperature under microwave irradiation for the synthesis reaction,
- computer-based means for controlling the system for complete autonomy during the process,

- a capping station for sealing the reaction tubes.

The device is appropriate for the synthesis of organic compounds, preferably low molecular weight compounds, for example, organic compounds generally having a molecular weight less than about 1000, more preferably less than about 500.

In a preferred embodiment, the device is capable of synthesizing in a fully automated manner more than one thousand compounds, more preferably more than 2000, and most preferably more than 4000 compounds. Several different tasks are carried out from the various functional units of the device in parallel, so that, for example, at least 4224 chemical reactions can be carried out in a fully automated manner and in a reduced amount of time. By "reduced amount of time", it is meant that the time is at least reduced to half or preferably a fourth of the time that would be necessary to perform each reaction one after another in a single microwave instrument.

The device enables full automatisation of the whole process. If required the reaction mixtures can be prepared under an inert atmosphere just before the microwave irradiation. A capping station is used to cap the microwave vials before microwave irradiation. A decapping station to decap the microwave vials after microwave irradiation can also be used if required.

Therefore, in a specific embodiment, the device of the invention, further comprises
- gassing station to fill vials with gas prior to the preparation of the reaction mixtures,
- decapping station to open the sealed reaction tubes,
- means for cooling the tubes after the reaction, and/or,
- means for washing dispensing needles of the pipetting station after use with appropriate solvents.

The device of the invention can comprise between 1 and 10, preferably between 3 and 5 microwave instruments, preferably 4, which can run in parallel. Any instruments appropriate for microwave-assisted chemical process can be used. In a preferred embodiment, one can use microwave instruments with remote access for having a network connection, such as for example those commercialized by Biotage.

Reaction vials of standard sizes of 0.2-0-5, 0.5-2, 2-5 or 10-20ml can be used. Preferably, the reaction vials are microwave vials with operating volumes of 0.5-5ml.

The storage system comprises racks for holding a plurality of reaction vials. The racks can be loaded semi-automatically using a PLC (programmable logic controller) interface into the storage system before the start of the process.

The storage system is for example, a deck capable of handling at least 44 racks, each rack holding 96 reaction vials, thus enabling the synthesis in a fully automated manner of at least 96x44 different compounds. Caps for sealing the reaction vials can also be placed in a cap stock at the capping station. The device further comprises computer-based means, i.e., software, for controlling the system for complete autonomy during the process. As used herein, complete autonomy means that all the reactions can be done in one run without human intervention, once the process is started. The device can therefore be run with an appropriate software from a single PC and the microwave instruments are then directly driven by the software through any type of connection, for example, an Ethernet connection.

The invention also relates to the use of the device as described above and in the example below, for synthesizing in a fully automated manner a plurality of organic compounds, preferably, more than 4000 compounds, with no human intervention. When carrying out the process for synthesis of a compound library with the device of the invention, the transport system does the moving of each individual reaction vial from one functional unit to the next.

In a preferred embodiment, the process for synthesis of a compound library comprises the following steps for each reaction vial:

(i) filling empty reaction vials with inert gas: Empty reaction vials are transferred from the storage system to the transfer/gassing station, and, if appropriate, are filled with inert gas, such as argon, or nitrogen. Any gassing station appropriate for transferring gas at a defined pressure in a reaction vial can be used. As an example, one can use the gassing station developed by Hamilton Bonaduz AG;
(ii) filling empty reaction vials with reaction solutions: The reaction vials are then moved in the transfer station to the pipetting position. At the pipetting station, the robot can remove the closure heads from bottles containing the reagents solutions, if required, and then pick up

needles or any appropriate dispensing means. Preferably, for air sensitive solutions, the solutions are stored in 100ml bottles with argon inlet and the bottles are opened just at the time of pipetting. The reagents solutions can be aspirated simultaneously and afterwards dispensed in the reaction vial. For rapidly evaporating solutions and solutions with very low viscosity, it may be necessary to use a separate aspiration/dispensing step. Preferably, the pipetting station comprises a pipetting robot with monitored air displacement. An example of such pipetting robot is the one commercialized by Hamilton Bonaduz AG. The pipetting robot can comprise a liquid level detection for conductive and polar liquids, such as a capacitive liquid-level detection (cLLD) and another liquid level detection for non-conductive and non-polar liquid, such as a pressure liquid level detection (pLLD);

(iii) filling reaction vials with inert gas: After dispensing the reaction solutions, the reaction vials are moved back to the gassing station and gassed again;

(iv) sealing the reaction vials: The reaction vials are then moved to the capping station. The capping station can perform the steps of cap feeding, putting cap on the reaction vial, and sealing the cap to the vials;

(v) microwave assisted synthesis reaction: The reaction vial is then transferred into one of the microwave instruments. The parameters needed for the reaction synthesis are set initially per vial individually;

(vi) decapping the reaction vials or storing into storage racks: The reaction vials are either directed to initial storage racks or moved towards a decapping station.

Each reaction vial will follow the above-described (i)-(vi) steps, but, since each step can not be carried out for each reaction vial at the same time, a preferred sequential order of each step for each reaction vial is selected such that the order and time of use of each functional unit for each reaction vial is optimized to minimize the duration of the whole process. In other words, instead of running through processes sequentially like a production line, the software can include a scheduler that insures that the robotic arm always carries the reaction vials in the various functional units of the factory where they are most needed, in order to optimally increase the speed of the whole process. More specifically, this makes genuine multi-tasking possible, i.e. several reactions can be performed simultaneously, each one under different conditions.

The process is thus optimized by such software by taking into accounts many parameters that cause different timing needs. The invention will be explained in more detail using exemplary embodiments and the associated figures.

LEGENDS OF THE FIGURE

Figure 1: Example of a device according to the invention. The different features shown in arrows are described in detail in Example 1.
Figure 2: Overview of the whole process

EXAMPLE

As shown in Figure 1, the device of the invention can comprise

- storage and transport systems (1), for example Rotzinger storage and transport system for up to 44 racks holding each 96 Biotage reaction vials (0.5-2ml and 2-5ml);

- instruments for microwave assisted chemical synthesis (2), for example, four Biotage single-mode microwave instruments (Biotage Initiator™);
- robotic system (3) to carry single Biotage microwave vials to the various functional units of the factory, for example Hamilton Microlab Swap 1400 with modified robotic hand;
- pipetting station (4) for the preparation of the reaction mixtures, for example, Hamilton Microlab STAR® 8 channels using 48 reusable steel needles and disposable tips;
- gassing station (5) to fill independently 2 microwave vials with argon and to bring them to the pipetting positions, for example, Hamilton transfer / argon gassing station.
- Afag capping station with caps conveyor (6); and,
- Afag decapping station (7).

The device of the invention may further comprise the following features:

- Carrier for six racks holding each 96 disposable tips;
- Carrier for thirty eight 100ml Schott bottles with CO-RE (Compressed O-Ring Expansion) technology automated closure heads;
- Carrier for four 96-well racks utilizing 10 ml tubes;
- Chemical resistant DMSO wash station with three wash modules holding each 8 needles with overflow sensor;
- Acetone wash station for the needles when pLLD is used and/or DMSO contamination should be avoided.
- Drying station for 3 × 8 = 24 needles;
- Trolley for 2 x 30l DMSO tanks for the needles wash station;
- Trolley for 60l waste tank including 60l safety container to avoid spilling;
- Operator panel; and,
- Ventilated hood.

The device can be run with an appropriate software from a single PC. The software includes a dynamic scheduler package which optimizes the process by taking into accounts many parameters that cause different timing needs. The microwave instruments are directly driven by the software through any type of connection, for example, an Ethernet connection. The

storage and transport system as well as the capper and decapper can be driven through a PLC (programmable logic controller).

In the proposed example, the user can choose between two different modes: the batch mode for library production or the open access mode for multiple user access and rapid reaction conditions optimization. For both modes, a user friendly GUI (Graphical User Interface) was implemented in order to facilitate the handling of the whole system.

Batch mode

The device can be run with the following batch mode. The one skilled in the Art will know how to adapt this process with different embodiments of the invention, for example, embodiments with similar instruments, commercialized by other companies, or with a different number of instruments and/or reaction vials.

An overview of the whole process is generally depicted in Figure 2.

The number of reactions processed per run depends on the number of microwave vials placed in the 96-well metal racks (maximum 44x96 = 4224 vials).
The user can run the whole process or only parts of it, e.g. only capping, microwave heating, no decapping, no pipetting etc...

Each microwave vial is tracked throughout its involvement in the process and its current status is written in a database. The user can follow the process on the PC screen.

1. Preparation

Work list:

The work list in which the user specifies the process which should be applied for each reaction vial of a defined run is generated on any user workstation with the help of a Graphical User Interface. In particular, the user enters the volumes to be pipetted, the main solvent to be pipetted and the conditions of the microwave reactions, argon, capping, decapping, acetone....

The work list imported into a database.

Caps:

The number of caps filled in the capping station is chosen according to the required autonomy.

Racks:

4x96 different stock solutions of 10ml volume are placed in the racks on the STAR deck.

Schott bottles:

The reagents solutions containing air sensitive solution are stored in the Schott bottles which are also placed on the STAR deck (38 Schott bottles of 100ml).

DMSO wash system:

The DMSO wash system includes the DMSO tanks fitted with a plunger including liquid level detection which are placed under the STAR deck and connected to the needles wash station and a waste container. The user checks that the 60l waste container fitted with a plunger including liquid level detection is empty.

Acetone wash station:

Acetone wash station is filled when pLLD is used and/or DMSO contamination should be avoided.

2. Rack Storage

The racks holding the empty microwave vials fitted with magnetic stirrers are loaded semi-automatically into Rotzinger storage system using the PLC interface. They are for example in 11 stacks of 4 racks each. At start two 96-well metal racks holding empty microwave vials are brought on the deck.

3. Pipetting

In case of working with air sensitive reagents, the user activates in the work list the gassing option. The first reactor is moved to the transfer / gassing station filled with argon for the chosen time. Next, the tube is moved in the transfer station to the pipetting position. The STAR removes all closure heads from the Schott bottles required for the current reaction and picks up the necessary number of needles from the wash station or disposable tips from the tips carriers. Schott bottles with an argon inlet were specially manufactured and these bottles are filled with argon before the STAR removes their closure heads.

The STAR aspirates the stock solutions from the racks and the reagents solutions from the Schott bottles sequentially, if the solvents to be aspirated have different properties or

simultaneously, if they have similar properties. Afterwards, the aspirated solutions are dispensed sequentially in the microwave vial. After pipetting, the Schott bottles are closed with the STAR and filled again with argon if required.

Rapidly evaporating solutions or solutions with very low viscosity are transported in a separate aspiration/dispensing step. This information is linked to the solvent properties given in the work list by the user.

The pipetting process has been optimized for the following solvents : acetone, acetonitrile, diethylether, dimethylformamide, dimethylsulfoxide, ethanol, isopropanol, methanol, methylene chloride, tetrahydrofurane, toluene, 1,2-dichlorethane, 1,2-dimethoxyethane, 1,4-dioxane, 1-methyl-2-pyrrolidone.

If the reagents placed in the Schott bottles are neither air sensitive nor volatile the user has the possibility to let the Schott bottles open during the all run.

After dispensing of all solutions in the microwave vials, the needles are washed in- and outside in one of the three modules of the DMSO wash station. If pLLD-compatible reagents are used, the needles are also washed with acetone and dried in order to avoid that any leftover causes an error in the pLLD detection. When working with cLLD and if DMSO contamination is an issue for the reactions, the same acetone wash process can be applied.

During the washing of one set of needles, the STAR arm continues pipetting with a clean set of needles from another washing module.

The user can also choose to work with disposable tips if the needles get clogged, e.g. when aqueous solutions of inorganic salts are aspirated and dispensed.

4. Capping

The scheduler optimizes the process to reduce to a maximum the time between pipetting and capping. Hence, in the scheduler, the transfer of the microwave vials from the transfer station after pipetting is set with high priority. After receiving the command to cap a microwave vial the capping station performs the following steps: cap feeding, placing cap on microwave vial and closing.

5. Microwave heating

Subsequently, the microwave vial is transferred by the SWAP robotic arm into one of the four microwave instruments and heated according to the parameters set in the initial work list. Upon cooling, according to the user input, the microwave vial can be moved back in the 96-well metal rack if the user wants to decap later.

6. Decapping

If decapping was set in the work list, upon cooling, the microwave vial is moved to the decapping station, opened and moved back in the 96-well metal rack

7. Back in the storage system

Once all the microwave vials from one 96-well metal rack have been processed, the metal rack moves automatically down.

Open access mode for optimization

In a specific embodiment, the device can also be run with an open access mode for optimization. Two 96-well metal rack are placed on the deck. In this mode, no rack transport, no pipetting and no gassing are taking place.

In this mode, each user has the possibility to run from 1 to 192 microwave reactions. The user can choose to bring his microwave vials already closed or to let them closed automatically with the capping station. The user can choose to take back his microwave vials closed or let them opened automatically with the decapping station. He enters all his parameters via the GUI. For the microwave reaction, the user enters the reaction temperature, the reaction time, the absorption level, the pre-stirring option (stirring prior to processing to improve the mixing of reagents) and can also choose the fixed hold time option (time countdown initiated when the target temperature is reached) or not.

The user has control over the vials that are queued and processed in turn. Through the GUI, the user knows the status of the 192 positions of the two accessible racks: in process, successfully processed, processed with error, free remaining positions.

After the microwave vials are processed, the user removes them manually from the 96-well metal racks and releases the positions through the GUI. This mode can be run in an endless

cycle. At any time new work lists can be added and are read within 15 seconds. The new tasks are scheduled within the current process.

For safety reasons, if necessary, the whole system is preferably in a ventilated hood with secure locked doors. Opening a door generates an immediate stop of the rack transport system, the capper and the decapper because these parts can be dangerous when moving. The process can be continued only if closing the door is confirmed at the PLC interface.

Besides, opening the STAR safety cover when the pipetting channels are in motion can generate an immediate stop of the system. The process can be continued only after a restart of the method.

Pausing the method allows the opening of the STAR safety cover for necessary handling of the pipetting system. Clicking pause again enables the method to be continued from where it had been paused.

If overpressure or sudden temperature raise is detected in a Biotage Initiator, the lid of the Initiator remains closed and the Initiator affected is taken out of the scheduling and the process is continued with three Initiators (or two or one).

CLAIMS

1. A device for the fully automated synthesis of a plurality of different organic compounds, comprising at least the following functional units:

- storage systems for a plurality of reaction vials and stock solutions,
- a transport system with a robotic arm capable of carrying a single reaction vial to the various functional units of the device,
- a pipetting station including a transfer station for the preparation of reaction mixtures in the reaction vials from stock solutions and reagents solutions,
- one or more microwave instrument for heating the reaction mixture under appropriate pressure and temperature under microwave irradiation for the synthesis reaction,
- computer-based means for controlling the system for complete autonomy during the process,
- a capping station for sealing the reaction tubes.

2. The device of Claim 1, further comprising

- gassing station to fill vials with gas prior to the preparation of the reaction mixtures,- means for cooling the tubes after the reaction,
- means for washing dispensing needles of the pipetting station after use with appropriate solvents, and/or,
- means for opening the reaction tubes.

3. The device of Claim 1 or 2, wherein several different tasks can be carried out from the various functional units in parallel so that at least 4224 synthesis reactions can be carried out in a fully automated manner and in a reduced amount of time.

4. The device of any of Claims 1-3, wherein the reaction vials are microwave vials with operating volumes of 0.5-5ml for example 5ml microwave vials.

5. The device of any of Claims 1-4, wherein the storage system comprises racks for holding a plurality of reaction vials, preferably at least 44 racks, each rack holding 96 reaction vials.

6. The device of any of Claims 1-5, comprising between 1 and 10 microwave instruments, preferably between 3 and 5, and more preferably 4.

7. The device of any of Claims 1-6, wherein the pipetting station comprises a pipetting robot with monitored air displacement.

8. The device of Claim 7, wherein the pipetting robot comprises a liquid level detection for conductive and polar liquids, such as a capacitive liquid-level detection and another liquid level detection for non-conductive and non-polar liquid, such as a pressure liquid level detection.

9. The device of any of Claims 1-8, wherein the computer-based means comprises a scheduler insuring that the robotic arm carries the microwave vials in the various functional units in a defined order that optimally increases the duration of the whole synthesis process.

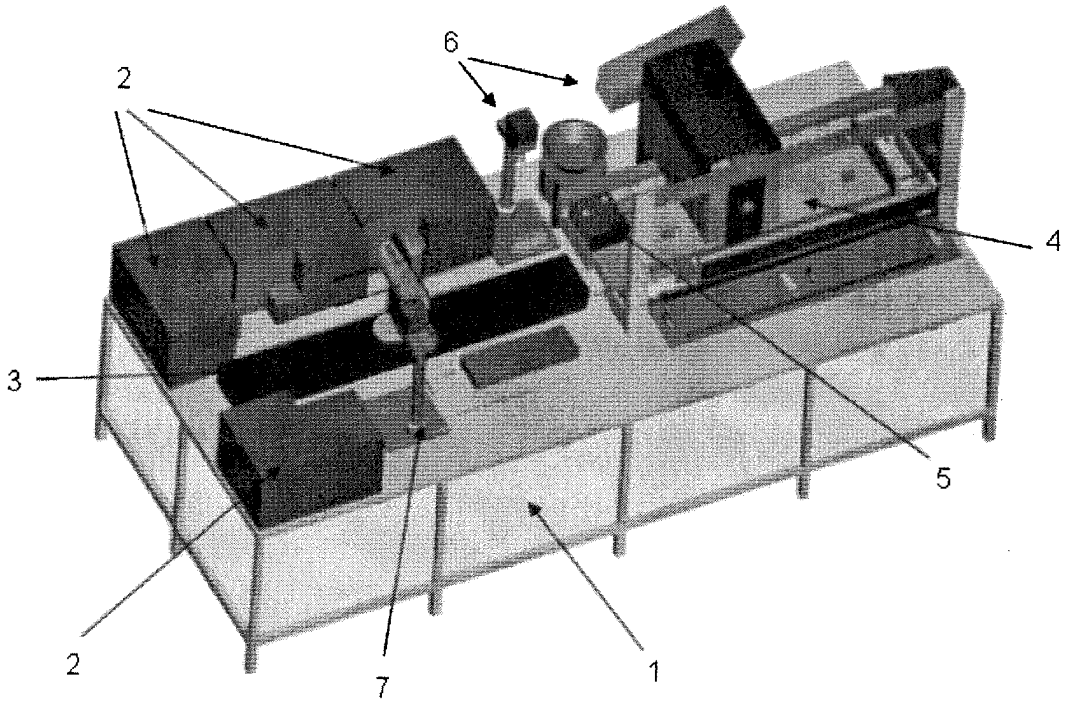
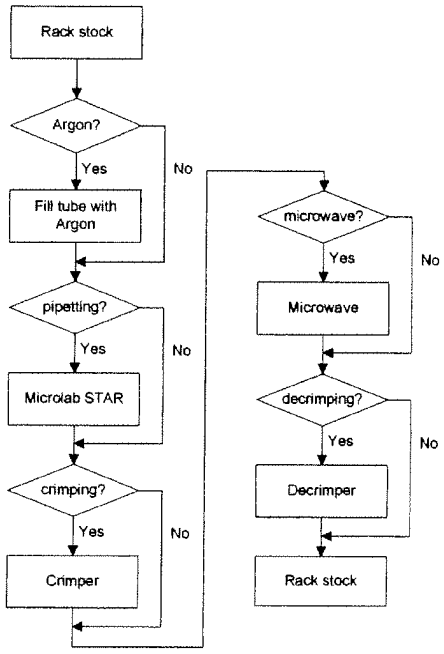


Figure 1

Figure 2


Rack stock
Argon?
Yes
No
Fill tube with Argon
pipetting?
Yes
No
Microlab STAR
crimping?
Yes
No
Crimper
microwave?
Yes
No
Microwave
decrimping?
Yes
No
Decrimper
Rack stock

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/056517

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01J19/00

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)
B01J G01N

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 practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/106891 A1 (FAGRELL MAGNUS [SE] ET AL) 12 June 2003 (2003-06-12) page 6, paragraph 95 page 7, paragraphs 114,115,117 page 1, paragraph 2; claims 1-28	1-9
X	US 2004/024493 A1 (FAGRELL MAGNUS [SE] ET AL) 5 February 2004 (2004-02-05) page 1, paragraph 5; claims 1-20 page 3, paragraph 35 - page 4, paragraph 37 page 7, paragraph 75 page 9, paragraph 125 - paragraph 126	1-9

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 October 2007	16/10/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Oenhausen, Claudia

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/056517

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/44741 A (ONTOGEN CORP [US]) 10 September 1999 (1999-09-10) page 6, line 22 - page 7, line 6; claims 1-12 page 7, line 21 - line 23 page 11, line 23 - page 12, line 3	1-9
X	JOSSES P ET AL: "Carrying out multiple reactions in organic synthesis with a robot" ADVANCES IN LABORATORY AUTOMATION ROBOTICS, ZYMARK CO., HOPKINTON, MA,, US, vol. 6, 1990, pages 47-59, XP000913653 ISSN: 1073-2195 figure 6	1-9
X	WO 2006/054964 A (METTLER TOLEDO [US]; BYSOUTH STEPHEN ROBERT [US]; HITE SIDNEY WILSON [) 26 May 2006 (2006-05-26) claims 1-18; figures 1-17	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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