Development and Application of a Solution-Phase Automated Synthesizer, 'ChemKonzert'

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In this paper we describe the development of a fully-automated solution-phase synthesizer, 'ChemKonzert' that can be used to prepare a wide variety of organic compounds. The automated synthesizer is ingeniously designed to perform most of the chemical reactions currently used by synthetic organic chemists and utilizes a centrifugal separator to efficiently achieve liquid-liquid extraction. The design of the hardware and software will be described in this paper, and several examples of organic reactions will also be presented as applications of the apparatus.

Key words solution-phase synthesis; automated synthesizer; centrifugal separator; ChemKonzert; application example

Recently, one of the trends in synthetic organic chemistry has been to use automated synthesizers for high speed synthesis of libraries of compounds, in order to meet the requirements for bio-assay studies.[1)] Combinatorial and high throughput parallel chemistry has become more popular, not only in pharmaceutical companies for developing drug candidates but also in chemical companies to develop catalysts and the like for making new materials.[2)]

Generally, chemists have to carry out many time-consuming and routine tasks, such as optimizing reaction conditions, synthesizing many derivatives, analyzing and purifying compounds. Various types of automated synthesizers have become commercially available, but most of them are focused on solid-phase chemistry. There are few reports on automated synthesizers for solution-phase synthesis because the work-up process is much more diverse than that of solid-phase synthesis and not easy to adapt for automation.[3,4)] To achieve a truly versatile and efficient automated synthesizer for organic synthesis, the ability to handle solution-phase chemistry is very important because most of the reactions that have been developed in organic chemistry are solution-phase ones.

In this report we describe the development of a solution-phase automated synthesizer, 'ChemKonzert®', and its application in various organic syntheses to verify the performance of the apparatus. There are two main uses of solution-phase automated synthesizers. Firstly, they are useful for the preparation of starting materials and building blocks for a lead generation. When chemists attempt to use combinatorial chemistry for solid-phase synthesis, they often face the problem of how to supply the large number of starting materials and building blocks. For example, in the case of a 2-step synthesis (target having molecular weight 300, target molecule volume 10 mg), at least 700 mg of the starting material will be needed for preparing 6 compounds (2×3), 12 g in the case of 100 compounds (10×10) and 120 g for 1000 compounds. The most time-consuming steps in a combinatorial synthesis using solid-phase synthesis are for the preparation of the starting materials and building blocks. An automated synthesizer for solution-phase synthesis would thus make an efficient platform for high speed synthesis of library compounds in combinatorial chemistry. Furthermore, reaction methods and conditions required for using a computer-controlled automated synthesizer can be left in each laboratory, and the reactions can be repeatedly run by any operator to get the same compounds in the future.

Secondly, automated synthesizers are beneficial because they allow the facile exchange of data such as reaction conditions, between research laboratories, especially regarding the lead optimization step. Medicinal chemists usually carry out reactions manually using simple glassware, but for manufacture, process chemists use instruments such as calorimeters to determine suitable reaction conditions for a large scale production. Thus, for process chemists, the data of reaction conditions coming from the research laboratory will be nothing more than a starting reference, and they will have to spend considerable time and effort into optimizing reaction conditions from the beginning. On the other hand, if medicinal chemists use an automated solution-phase synthesizer, the data exchange is very efficient, and the process is scaled-up smoothly and reliably, eliminating differences that inevitably arise from human operators.

Results and Discussion

ChemKonzert is designed on a 'unit concept', which means the instrument is divided by functions. For example, there is a solvent unit for holding reaction solvents and a reagent unit for reaction reagents. A schematic diagram of the 'unit concept' is shown in Fig. 1. Other units are for, reaction, transfer, separation, drying, collection, washing and waste, as shown in Fig. 2. In addition, each of the solvent, reagent and reaction units can easily be increased to 3 units. By applying this 'unit concept', we were able to construct the system to be very user friendly and easily adaptable to customer requirements.

One of the most characteristic features in ChemKonzert is that a centrifugal separator is installed in the synthesizer to overcome problems due to emulsion formation in the extraction process, and the same centrifugal separator can also be used as an independent instrument. After using the centrifugal system to separate an emulsion into its component aqueous and organic parts, these are divided by using the different

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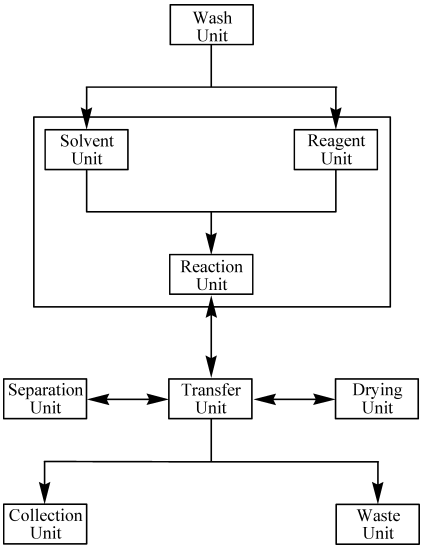

Fig. 1. Schematic Diagram of the Units

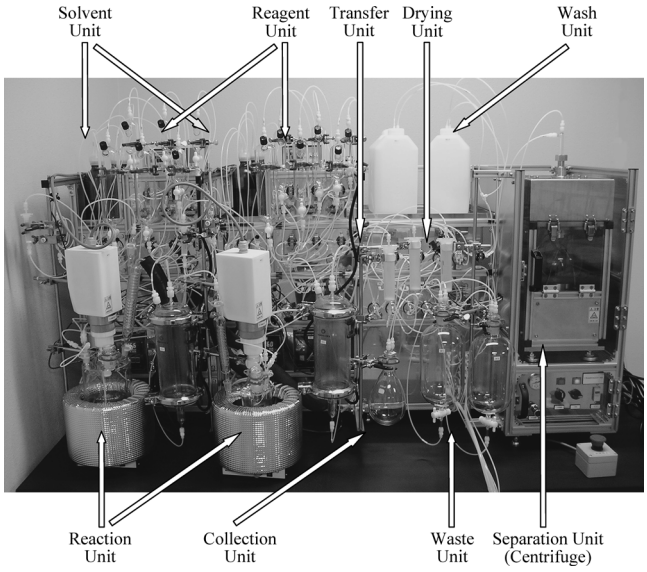

Fig. 2. Photograph of ChemKonzert

electric conductivity of the two layers to detect the interface between them. The system of flow-line type instruments uses many valves to connect each unit. Rotary valves (UV-9444P, UV-9844P, UV-9144P and UV-9454S, Uniflows Co., Japan) are adopted in this instrument for three reasons; firstly to reduce the size of the system. By using rotary valves, the dimensions of the system can be kept relatively small (1550(W)×540(D)×730(H)), while including 2 reaction units, 2 solvent units, 2 reagent units and a work-up unit, as shown in Fig. 2. Secondly, the electrical circuit boards and the Teflon® flow-lines can be well separated to guard against potential fire risks. Thirdly, easy maintenance of the system for the user is based on all flow-lines of the system being arranged for access from the front of the system.

In ChemKonzert, each unit and all the glassware are connected by Teflon tubes, which make up the "flow-line" system. This flow-line system is easy to keep under inert atmosphere during experiments, but washing of the whole system is necessary and it is very difficult to handle solid reagents. To handle the washing requirement, two solvent reservoirs are equipped for washing all the glassware and Teflon tubes, with both water and acetone. Subsequently, the lines are dried using the vacuum pump (MZ-2C, Vacuumbrand, GMBH+CO KG), which is also used for transferring the solvents, reagents, and reaction mixtures.

The flow-lines and the insides of the solenoid valves (MTV-02R-NM6G (DC-24V), MTV-2R-NM6G (DC-24V) and MTV-3R-NM6G (DC-24V), Takasago Electric Inc., Japan) are all made of Teflon. The inside of the rotary valve is made of PPS (polyphenylene sulfide) and Teflon. The reaction flask, the separation funnel and the centrifuge flask are made of PYREX® glass. In addition, the reaction unit flasks can be easily connected to other glassware, such as distillation adaptors, through the use of 'quickfit' (15/25 or 25/42) joints. The transferring of the reagents/solvents/reaction mixtures is carried out using a vacuum pump, which avoids the risk of trouble, such as the bursting of tubes and leakage of solvents/reagents that may occur if a syringe pump or nitrogen pressure is applied, or a tube becomes clogged. In addition, this system can be used for concentration under vacuum and photosensors (EE-SPX613, OMRON Co., Japan) are installed to detect the flow of liquid in the Teflon tubes. For safety, the system will be automatically shut down in the event of an earthquake, and also an emergency button allows the system to be immediately shut down. In the electrical system, all temperature controllers (E5AN, OMRON Co., Japan) and solid state relays (G3NA-210B (DC-24V), OMRON Co., Japan) that are used have been designed to be spark-free.

Construction and Function of Units. Solvent Unit The solvent unit has three commercially available solvent bottles (500 ml or 1 l) and one measuring tube (MT, 20 ml) to measure the solvent volume. For example, if the reaction requires 40 ml of the solvent, the system will fill the set amount (20 ml), deliver the solvent, and then the system will fill the MT again and deliver to the reaction flask (totally 40 ml). The MT can be easily changed to handle different volumes, if necessary, appropriate for the desired reaction scale.

Reagent Unit The reagent unit has three reagent reservoirs and three wash solvent reservoirs. The entire reagent that is set in the reagent bottle will be transferred to the reaction flask. This method is more useful than using an auto-sampler because auto-samplers require some dead volume and the entire reagent in the vials cannot be delivered. The reagent reservoirs can be easily replaced with new ones, which may be pre-filled in another place, such as a laboratory fume hood.

Reaction Unit This unit usually consists of two reaction vessels. The reaction unit has one commercially available reaction flask (maximum 1 l) with an oil bath, one filtration flask and two thermometers to measure the inside and outside temperature of the reaction flask. Each reaction flask has one reflux condenser, one mechanical stirrer, and five Teflon tube flow-lines, which come from the reagent, solvent and washing units and are connected to the transfer unit. Also, one spout allows for the addition of solid reagents or the taking of small portions of the reaction mixture for monitoring by TLC, if required. A filtration flask is set next to the reaction flask, for collecting crystals or precipitates that may be generated after or during the reaction. In addition to solid fil-

trates, this system can also handle scavenger resins, which may be put into the filtration flask as part of the work-up of the reaction mixture. Temperature control of the reaction flask is performed locally with two thermostatic controllers, one for measuring the inside of the reaction flask and another for measuring the outside.

The dropping speed of solvents and reagents can be controlled under inert atmosphere, by opening and closing the valve that is located between the reagent or solvent unit and the reaction unit. In addition, solvents and reagents can be dropped while keeping the desired temperature within ±2 °C in the apparatus. A feature that is very useful for both temperature controlled reactions, such as anion type reactions, and the quenching of reactions, which often benefits from temperature control to prevent undesirable decomposition of the products. After finishing the reaction, the reaction mixture can be quenched in the flask by delivering the quenching solution from the solvent unit. Then the mixture can be transferred to the separation unit, drying unit or collection unit, and through the transfer unit to complete the work-up of the reaction. Re-extraction of the separated aqueous layer and washing of the combined organic layer can also be performed in the reaction flask. For achieving efficient and effective stirring, a modified magnetic-induced mechanical stirrer is used in each reaction vessel.

Transfer Unit This unit is situated between the reaction unit and the separation unit, the drying unit and the collection unit. The Transfer unit allows the destination of the reaction mixture in the reaction flask to be varied between the separation unit, the drying unit, the collection unit or another reaction unit.

Separation Unit The unit is equipped with two separation flasks and a centrifuge instrument.[5] After the reaction mixture is quenched, the mixture is transferred into the centrifuge through the transfer unit. A common difficulty encountered when using automated separation is that it may take an excessively long time for the mixed phases to separate. Indeed, it may be found that some mixtures (*e.g.*, aqueous alkaline/CH_2Cl_2) form particularly stable emulsions that do not separate even after several hours. In order to overcome this problem we devised an automated means to separate emulsified extracts, using centrifugal force to rapidly separate and divide the individual phases.[6] The centrifugal separating unit offers the ability (1) to shorten the time, (2) to avoid the need to add another reagent or solvent and (3) to handle volumes of about 50 ml to 2 l.

The emulsified sample is transferred into a robust round glass flask that is spun at high speed (maximum 2000 rpm). As the flask is rotated, the emulsified sample spins and the two phases separate under the centrifugal force that is created. The bottom of the flask is connected to the central motor and the top is held by a collar containing ball bearings. The flask can be easily removed for maintenance by unscrewing the top holder. In order to transfer solutions into the flask when it is stationary, the top cap is pushed down onto the mouth of the flask to form a seal. Three tubes are fixed to the cap, one extending to the bottom and the other two into the top of the flask. Using these tubes it is possible to apply vacuum or pressure to accomplish the transfer of solutions. A window is fitted in the front panel of the unit to allow visual monitoring of the separation, which is useful during development work before unattended full automation is attempted. The power to the unit is switched on with one relay and the speed can be set at 0—2000 rpm, either manually or from the control computer. One further relay switch controls a solenoid that pushes the cap down onto the mouth of the flask to form seal. After the emulsified sample is transferred to the separating flask and the phases are separated, the sample is transferred out of the flask passing a flow-type conductivity sensor and a conductivity meter (WBM-100, DKK TOA Co., Japan), which can detect the boundary between the phases and then control a solenoid valve to direct the phases into separate collection flasks.

Drying Unit The drying unit is equipped with three drying tubes. Usually anhydrous sodium sulfate is used as a drying reagent. For easy use, this system is compatible with commercially available disposable tubes (5010-19111, Varian Instruments, U.S.A.), and a variety of columns, such as silica gel for short column purification, may be used.

Collection Unit This unit is equipped with three flasks to collect the desired fractions or final products.

Washing Unit This unit is equipped with two solvent bottles, one for water and another for organic solvent such as acetone or methanol. The unit is connected to the solvent unit to allow washing of the MTs and also to the reagent unit to enable washing of the reagent bottles, if required. After washing the MTs or reagent bottles, the wash solvent is transferred into the reaction unit to wash the flow-lines and reaction flasks. After washing all the tubes and glassware using water and acetone, the system can perform drying of all the tubes and glassware, using a vacuum pump and dry air or inert gas.

Waste Unit This unit is equipped with a cold trap, vacuum pump, two waste bottles, a recycling chiller and seven valves for the coolant. A waste solution, such as the solvent that has been used for washing the system or waste layer after an extraction process, is transferred into the waste bottles through a cold trap. The coolant continually flows inside the cold trap from the time the instrument is turn on. If the reaction unit requires cooling or reflux, the control system will direct the flow of the coolant using the valves in this unit, to cool the oil bath or the reflux condenser.

Computer Control System The control software, 'KonzertMeister', is well designed for easy operation by organic chemists. The concept of the software is based on using the familiar chemical terms that appear in experiments, as the names of commands, for example, 'Extraction', 'Stir Reaction Flask', 'Separation' *etc*. For delivering solvents or reagents, the commands use abbreviated forms such as 'RR1-RF1', which means transfer the solvent/reagent in the reagent bottle 1 (RR1) to the reaction flask 1 (RF1). The transcription system is very simple and easy and soon becomes familiar to organic chemists. The commands, called 'Steps' in the software, are pre-prepared and available to easily make into a sequence as an experimental protocol for a reaction, simply by double clicking on the required 'Steps'. In addition, if the user wants to modify the step or make a new step, the software can be easily modified. A record of temperature is sometimes important, so the software records both inside and outside temperatures for the reaction flasks, once every minute.

Fundamental Reaction Applications Some typical re-

actions were carried out to demonstrate the performance of the apparatus. The first application was the protection of an amino functional group, as shown in Fig. 3,[7] which demonstrated the usefulness of the filter attached to the reaction flask and the dropwise addition of reagents from the reagent unit. As an example of the protection of only one amino group of a compound containing two equivalent amino groups, the di-amino compound, ethylenediamine, was protected with a single *t*-butoxycarbonyl (Boc) group. In this reaction, the byproduct (di-Boc derivative) was crystallized during the work-up process by the addition of water, which then facilitated its separation and removal using the filter.

The next application shows the protection of a hydroxyl group with a tetrahydropyranyl (THP) group, which demonstrates the apparatus for starting material synthesis. Especially, the protection of only one functional group, a hydroxyl group in this case, in a compound having two equivalent functional groups is very useful for the synthesis of building blocks in combinatorial chemistry. In this manner, useful starting materials can be obtained in a straightforward and reliable manner using the synthesizer. The protection reaction of an alcohol is reported as a two phase reaction and the yield drops down if the mixing is not enough.[8] Thus, this reaction demonstrates the stirring and work-up performance of the instrument, as shown in Fig. 4.

Another protection reaction, that of an alcohol with a *t*-butyldimethylsilyl (TBS) group using NaH, was carried out to demonstrate the ability to keep an inert environment in the system, as shown in Fig. 5.[9] In addition, the handling of NaH was shown, including the ability to wash the reagent with dry hexane before use, in order to clean it.

A C–C bond formation reaction was carried out as shown in Fig. 6. Masamune reaction requires the activation of each starting material before starting the reaction. Each starting

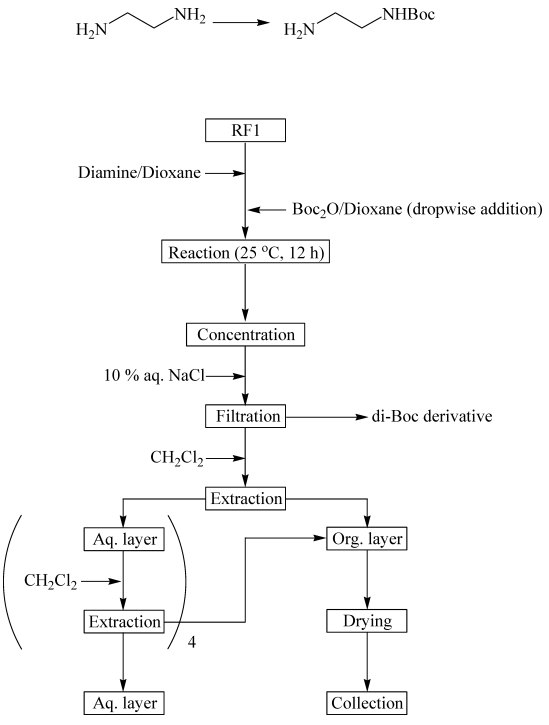

Fig. 3. Flowchart for the Synthesis of (2-Amino-ethyl)-carbamic Acid *t*-Butyl Ester

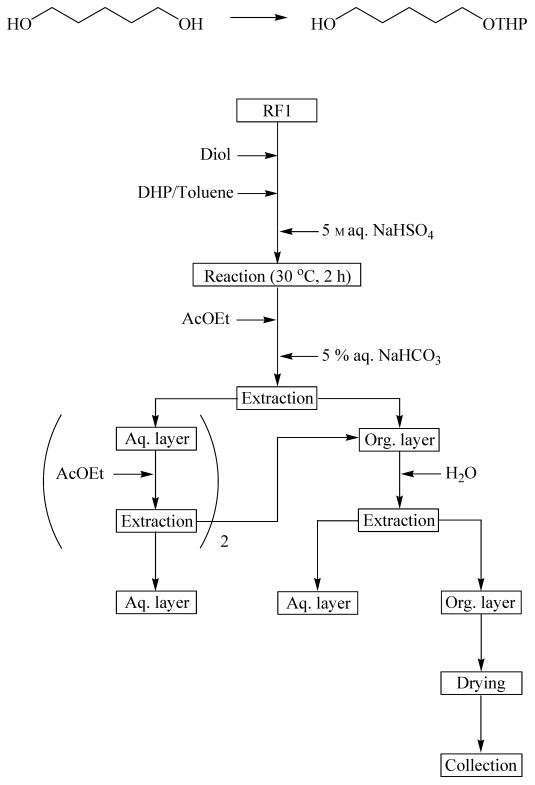

Fig. 4. Flowchart for the Synthesis of 5-(Tetrahydropyran-2-yloxy)pentan-1-ol

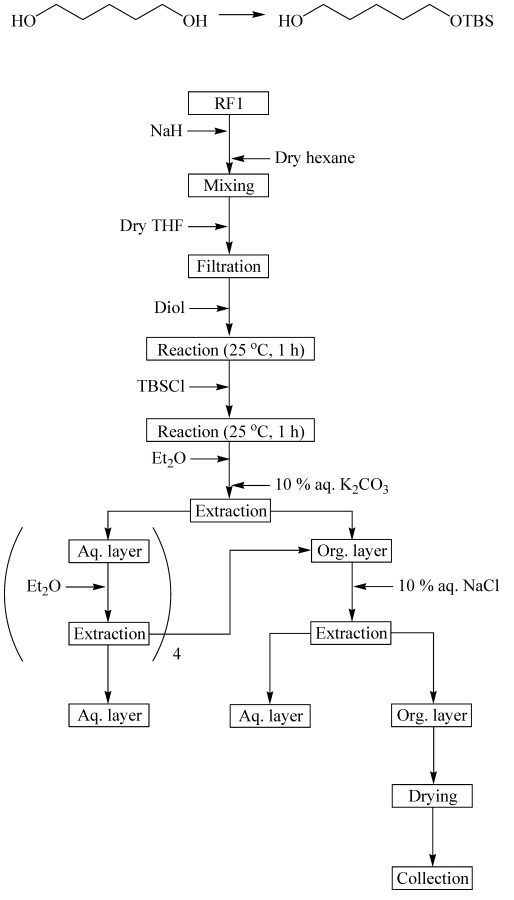

Fig. 5. Flowchart for the Synthesis of 5-(*t*-Butyldimethylsilanyloxy)pentan-1-ol

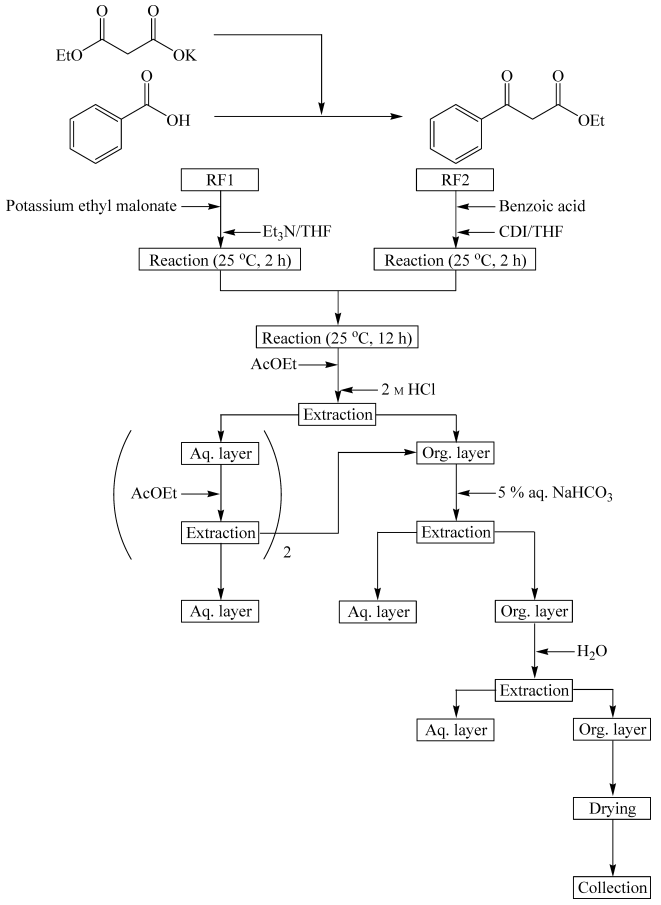

Fig. 6. Flowchart for the Synthesis of 3-Oxo-3-phenylpropionic Acid Ethyl Ester

material needed to be activated in different reaction flasks, before being mixed to perform the Masamune reaction. With this reaction, it was possible to demonstrate the usefulness of the apparatus with two reaction flasks and show their simultaneous use.

A two step reaction was also carried out in this apparatus. One of the important features of ChemKonzert is that it can perform multi-step synthesis. The first step was to form an O–C bond (O-alkylation reaction) under reflux conditions and the next step was to perform a hydrolysis reaction using a different solvent, as shown in Fig. 7. In addition, the heating and filtration ability of the instrument was demonstrated, as the reaction required reflux and the main product was generated as a solid.

After several types of reactions under inert environment had been successfully carried out in the instrument, we attempted to demonstrate the use of moisture sensitive reagents such as Grignard reagents, as shown in Fig. 8. The experimental protocol included a quenching step during the work-up process, where the reaction mixture was poured into an aqueous layer. One reaction flask was used to perform the reaction and the second flask was used for the work-up. The instrument does not have a purification unit but the instrument has drying tubes to dry the organic layer, and these tubes can also be exchanged for commercially available silica gel tubes for short column purification. Anhydrous sodium sulfate was put into the first tube to dry the organic layer and silica gel was put into the second tube to purify the organic layer. After

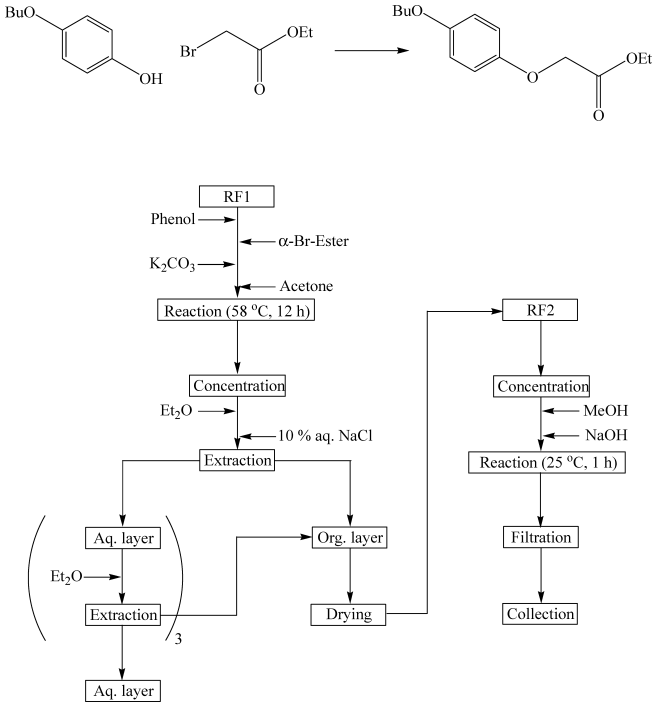

Fig. 7. Flowchart for the Synthesis of (4-*t*-Butoxy-phenoxyl)-acetic Acid

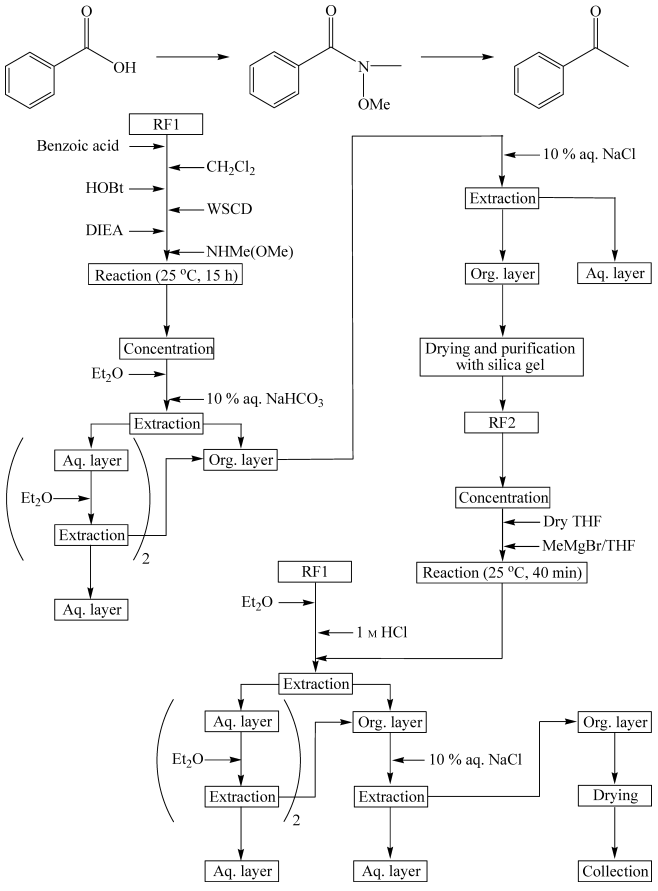

Fig. 8. Flowchart for the Synthesis of Acetophenone

Weinreb amidation, the organic layer was dried and purified through the tubes. Finally, the organic layer was concentrated, in order to change the solvent to perform the Grignard

reaction.

Conclusion

We have designed and constructed ChemKonzert and the accompanying control software for automated solution-phase synthesis. This synthesizer is designed for flexible set up, based on a unit concept, easy maintenance, and user friendly software. The operating software for the system has been designed to be intuitive for organic chemists, to allow operation of the automated synthesizer using protocols that are familiar and based on traditional synthesis techniques.

It is very important to carry out several types of actual reaction to demonstrate the performance of the instrument, and the following have been shown; (1) two phase reaction to demonstrate mixing ability, (2) temperature controlled reaction at reflux and 0 °C, (3) handling of air and moisture sensitive reagents, (4) handling precipitates after reaction is completed, (5) a continuous two step reaction. The results of each reaction have shown that the synthesizer is useful and reliable for organic chemists. In addition, the work-up process was performed automatically and the centrifugal separator system worked well for all of the reactions. Thus the automated synthesis system was shown to be capable of preparing various types of organic compounds. The instrument can perform all the typical solution-phase reactions used in the pharmaceutical and chemical industries that do not require the use of high pressures or automated handling of solids.

During the last 100 years, an enormous number of solution-phase reactions have been developed by many organic chemists, throughout the world. With an automated solution-phase synthesizer such as ChemKonzert, it is now possible for all scientists, not only specialist organic chemists, to exploit the vast wealth of knowledge and produce useful organic compounds. In fact, efficient preparations of key intermediates for syntheses of TAXOL® and the 9-membered masked enediyne have recently been achieved by using ChemKonzert.[10,11] It is indicated that the automated synthesizer can be utilized in broad area of organic syntheses.

Experimental

Materials and reagents were purchased as follows: solvents were of special or first grade from Tokyo Kasei Kogyo Co., Ltd., Wako Pure Chemical Industries Ltd., and Aldrich Chemicals Ltd. Short column chromatography was performed on Silica Gel 60 N, purchased from Kanto Chemical Co.

Synthesis of (2-Amino-ethyl)-carbamic Acid *t*-Butyl Ester The reaction was carried out as shown in Fig. 3. Starting material, ethylenediamine (5.25 g) in 32 ml of dioxane was delivering from the reagent bottle to the reaction flask (RF1). Di-*t*-butyl dicarbonate, (Boc_2O; 2.27 ml) in 31 ml of dioxane was dropped from the reagent bottle to the reaction flask over 2.5 h at 0 °C. After delivering the reagent, the reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated *in vacuo* in the reaction flask. Then byproduct (di-Boc derivative, 55.5 mg, 2%) was filtered off using the filtration unit, after 10% aq. NaCl (40 ml) was added from the solvent bottle to the reaction flask. The remaining reaction mixture was transferred to the centrifuge through the transfer unit and the separated aqueous layer was extracted with CH_2Cl_2 five times (40 ml×5). The combined organic layers were collected into the collection flask through the drying tubes filled with anhydrous sodium sulfate. The organic layer was concentrated *in vacuo* to give 1.49 g of (2-amino-ethyl)-carbamic acid *t*-butyl ester (isolated yield, 93%; cf. yield in literature,[7] 90%).

Synthesis of 5-(Tetrahydro-pyran-2-yloxy)pentan-1-ol This reaction was carried out as shown in Fig. 4. The reaction was started after adding the starting material, pentane-1,5-diol (1.04 g) to the reaction flask (RF1) manually, and the reagents, 3,4-dihydro-2*H*-pyran (DHP; 3 ml) in 57 ml of toluene and 5 M aq. sodium hydrogen sulfate (2 ml) were delivered to the reaction flask from the reagent bottles. The reaction mixture was stirred at 30 °C for 2 h. After adding 100 ml of AcOEt to the reaction mixture, 5% aq. sodium hydrogen sulfate (40 ml) was delivered from the reagent bottle to the solution with stirring, to quench the reaction. Then the mixture was transferred to the centrifuge through the transfer unit and separated into two layers. The separated aqueous layer was extracted with AcOEt twice (40 ml×2). The combined organic layers were washed with water (20 ml), and then collected into the collection flask through the drying tubes filled with anhydrous sodium sulfate. Finally, the organic layer was concentrated *in vacuo* using a rotary evaporator to give 1.68 g of 5-(tetrahydro-pyran-2-yloxy) pentan-1-ol (isolated yield, 89%; *cf.* yield in literature,[8] 92%).

Synthesis of 5-(*t*-Butyldimethylsilanyloxy)pentan-1-ol The reaction was carried out as follows, and as shown in Fig. 5. Before starting the reaction, the instrument was slightly modified by adding a Teflon filter and a Teflon tube that reached to the bottom of the reaction flask (RF1) and connected to the transfer unit. NaH (0.84 g) solid was placed in the reaction flask on the filter and then the reaction flask was kept under inert atmosphere. Dry hexane (20 ml) was delivering from the solvent bottle to the reaction flask. After mixing, hexane was removed from the reaction flask to the waste bottle through the filter. Tetrahydrofuran (THF) (40 ml) and the starting material, pentane-1,5-diol (2.02 ml) in 20 ml of THF were delivered from a solvent bottle and a reagent bottle, respectively, to the reaction flask. The reaction mixture was stirred at 25 °C for 1 h, and then *t*-butyldimethylsilyl chloride (TBSCl; 2.91 g) was manually added to the reaction flask through the spout. The reaction mixture was diluted with Et_2O (120 ml), and then quenched by 10% aq. K_2CO_3 (140 ml). After separating the two layers, the aqueous layer was extracted with Et_2O four times (100 ml×3). The combined organic layers were washed with 10% aq. NaCl (100 ml), collected into the collection flask through the drying tubes filled with anhydrous sodium sulfate. The organic layer was concentrated *in vacuo* to give 3.85 g of 5-(*t*-butyldimethyl-silanyloxy) pentan-1-ol (isolated yield, 92%; *cf.* yield in literature,[9] 87%).

Synthesis of 3-Oxo-3-phenylpropionic Acid Ethyl Ester The reaction was carried out according to the flowchart shown in Fig. 6. Potassium ethyl malonate (4.08 g) was put into the reaction flask (RF1) and benzoic acid (2.44 g) was put into the reaction flask (RF2) by manual operation. Triethylamine (6.65 ml) in 20 ml of THF was delivered from the reagent bottle to RF1, and then magnesium chloride (3.43 g) was put into RF1 by manual operation through the spout of the reaction flask. The mixture was stirred at 25 °C for 2 h. Meanwhile, 1,1′-carbonyl-bis-1*H*-imidazole (CDI; 3.90 g) in 60 ml of THF was delivered from the reagent bottle to RF2, and the mixture was stirred 25 °C for 2 h. The solution in RF1 was transferred to RF2 to carry out the Masamune reaction. The reaction mixture was stirred at 25 °C for 12 h, diluted with AcOEt (200 ml), quenched by addition of 2 M HCl (100 ml), and then separated into organic and aqueous layers. The separated aqueous layer was extracted with AcOEt twice (100 ml×2). The combined organic layers were washed with 5% aq. $NaHCO_3$ solution (100 ml) and water (60 ml), and then transferred to the collection flask through the drying tubes filled with anhydrous sodium sulfate. The organic layer was concentrated *in vacuo* to give 3.67 g of 3-oxo-phenyl-propionic acid ethyl ester[12] (isolated yield, 96%).

Synthesis of (4-*t*-Butoxy-phenoxy)-acetic Acid The reaction was done as shown in Fig. 7. The starting material, 4-butoxy-phenol (2.02 g) was put into the reaction flask (RF1) by manual operation, and then ethyl bromoacetate (1.34 ml) and K_2CO_3 (5.09 g) were also put into the same reaction flask by manual operation. Acetone (50 ml) was delivered from the solvent bottle to RF1. The reaction mixture was stirred at 58 °C for 12 h, and then concentrated *in vacuo* in RF1. The residue was diluted with Et_2O (60 ml) and quenched by addition of 10% aq. NaCl (60 ml). The separated aqueous layer was extracted with Et_2O three times (40 ml×3). The combined organic layers were transferred to RF2 through the drying tubes filled with anhydrous sodium sulfate. The organic layer in RF2 was then concentrated *in vacuo* in order to change the reaction solvent from Et_2O to methanol (60 ml). Aqueous 2 M NaOH solution (40 ml) was added dropwise from a reagent bottle to RF2 and the mixture was stirred at 25 °C for 1 h. The solid was filtered using the filtration unit to give 2.36 g of (4-butoxyphenoxy)acetic acid[13] (isolated yield, 87%).

Synthesis of Acetophenone The first reaction was carried out as shown in Fig. 8. Using the reaction flask 1 (RF1), benzoic acid (1.22 g) and CH_2Cl_2 (60 ml) were delivered from the reagent and solvent bottles to RF1. 1-Hydroxybenzotriazole (HOBt; 2.03 g) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (WSCD; 3.15 g) were added to RF1 by manual operation. *N*,*N*-Diisopropylethylamine (DIEA; 2.55 ml) and *N*,*O*-dimethylhydroxylamine (NHMe(OMe); 1.47 g) were delivered to RF1 by manual operation at 0 °C.

The reaction mixture was stirred at 25 °C for 15 h, and concentrated *in vacuo* in RF1. The residue was diluted with Et_2O (200 ml) and quenched by addition of 10% aq. $NaHCO_3$ (40 ml). The mixture was separated into two layers and the separated aqueous layer was extracted with Et_2O twice (40 ml×2). The combined organic layers were delivered to the reaction flask 2 (RF2) after washing with 10% aq. NaCl (40 ml), drying and purifying through tubes packed with silica gel. After transferring the organic layer to RF2, the RF1 was washed with water and acetone delivered from the washing unit. After drying RF1 flask under reduced pressure, Et_2O (100 ml) and 1 M HCl (60 ml) were delivered from the solvent bottles to RF1 and the mixture was stirred at 0 °C. Dry THF (80 ml) was delivered to RF2 and cooled to 0 °C after the organic layer in RF2 was concentrated. After stirring at 0 °C, methyl magnesium bromide (5.6 ml) in 20 ml of THF (0.1 M) solution was added dropwise into RF2 at 0 °C. The reaction mixture was then stirred at 0 °C for 40 min, before being quenched by transferring the reaction mixture from RF2 to RF1. The separated aqueous layer was extracted with Et_2O twice (40 ml×2). The combined organic layers were washed with 10% aq. NaCl (40 ml), and then collected into the collection flask through another drying tube filled with anhydrous sodium sulfate and then concentrated *in vacuo* using a rotary evaporator to give 0.72 g of acetophenone[14] (isolated yield, 60%).

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