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Method for multipolymer synthesis of organic compounds

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***ABSTRACT**: A broad range of organic synthesis reactions have been conducted by means of a process using two polymeric supports, each carrying different reactive species. A liquid medium containing a specifically selected intermediate reactant, in a solvent, is circulated between the supports in order to remove the reactive species from the first support by reaction with the intermediate, and permit the reactive species thus removed to react with the reactive species of the second support, at the same time regenerating the original intermediate reactant. This circulation continues until the second support is suitably loaded with the reaction product, at which time the circulation is slopped and the reaction products separated and recovered. The process may be carried out in an automated apparatus in which sensors are placed at the entrance and exit of the column carrying the second polymeric support. The sensors are capable of sensing the relative presence of the intermediate reactant. When the same content of intermediate reactant is sensed at both the entrance and exit of the second column, the circulation will be automatically stopped as this will indicate complete loading of the second column.*
***KEYWORDS**: Multipolymer Synthesis, Organic Compounds, organic synthesis, polymeric supports.*

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I. INTRODUCTION

The test involves the generation of a reactive intermediate from an insoluble polymeric precursor and its detection by trapping on a second solid phase. This method is especially useful for the detection of intermediates in nucleophilic catalysis. The same principle was applied by Rebek to reactions involving metaphosphates, cyclobutadiene and in phosphate transfer reactions [1-3]. Except for certain specific acylation reactions; none of the three-phase reactions of Rebek disclose regenerable intermediates. Although similar in principle to the reaction carried out in the device of the present invention, Rebek et al describes an analytical reaction with minimum quantities of reactants without envisaging applicability for synthetic purposes. Moreover, in the case of Rebek, the two polymers were mixed together or were separated by sintered glass fit and the reactive intermediate formed was transferred from one polymer to the other. This system does not permit monitoring and automation of the reaction [4-9].

II. METHOD AND DISCUSSION

Rih e present invention provides a broadly applicable method of synthesis of organic compounds. It is another object of the present invention to provide an apparatus for the automatic synthesis and recovery of organic compounds. These and other objects of the present invention are attained through the use of first and second polymeric supports each carrying different reactive species. A liquid medium containing a specifically selected intermediate reactant, in a solvent, is circulated between the supports in order to remove the reactive species from the first support by reaction with the intermediate, and permit the reactive species thus removed to react with the reactive species of the second support, at the same time regenerating the original intermediate reactant. This circulation continues until the second support is suitably loaded with the reaction product, at which time the circulation of the intermediate reactant is stopped and the reaction product separated and recovered from the second support. The obtained reaction product will be free of the original reactant from the first support and the intermediate reactants, thus permitting selective and high yield synthesis.

The initial reaction product on the second polymeric support may itself be used as a new reactive species, without separating it from the polymeric support. A new first polymeric support/reactive

species can be substituted for the original first Polymeric support to add another new reactive species on the second support. In this way longer chain products, as, for example, polypeptides or polynucleotides may be synthesized by the method of the present invention.

The process of the present invention is preferably carried out in an apparatus which permits automation of the process. In this apparatus the two polymeric supports are each placed into respective columns between which the intermediate reactant may circulate. Two sensors capable of sensing the relative presence of the intermediate reactant are placed respectively at the entrance and exit of the second polymeric column. When the same content of intermediate reactant is sensed at both the entrance and exit of the second column, this will indicate completion of loading of the second column and the beginning of the next synthesis phase or the separation and recovery phase. A microcomputer is provided to react to this indication of completion by closing of appropriate to permit completion of the process. The sensors may be capable of quantitative analysis of the concentration of the intermediate reactant, thus providing a continuous direct record of yield.

The present invention will be better understood upon consideration of the following detailed description in conjunction with the attached drawings, in which:

Fig. 1 is a schematic illustration of the apparatus of the present invention;

Fig. 2 is a schematic illustration of an apparatus in accordance with the present invention shown in an initial stage of peptide synthesis;

Fig. 3 is a schematic illustration of the apparatus of FIG. 2 in a later stage of peptide synthesis; and Fig. 4 is a schematic illustration of an apparatus for the synthesis of polypeptides, such as enkephalin.

DESCRIPTION OF THE DRAWING

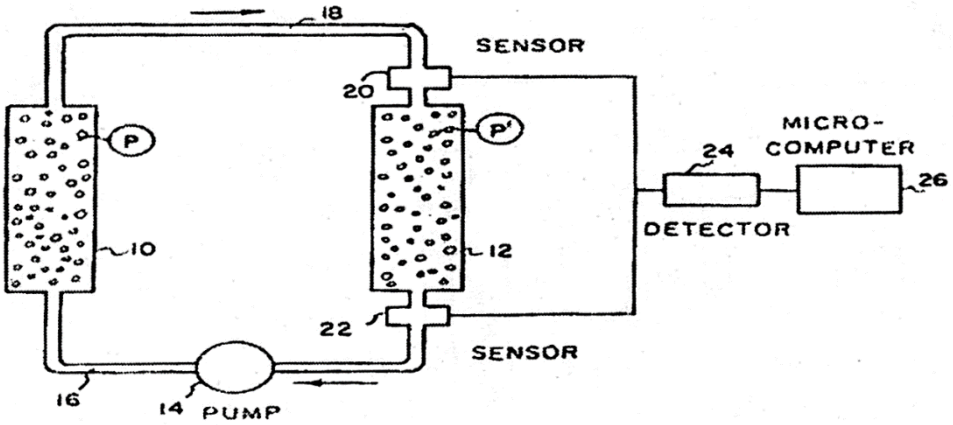


Fig.-1

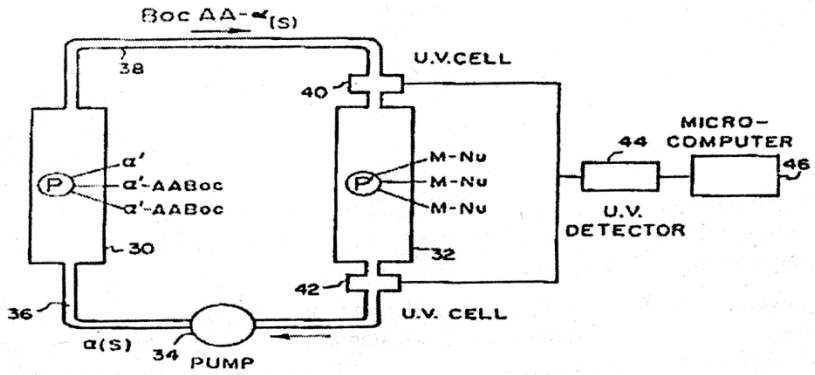


Fig.-2

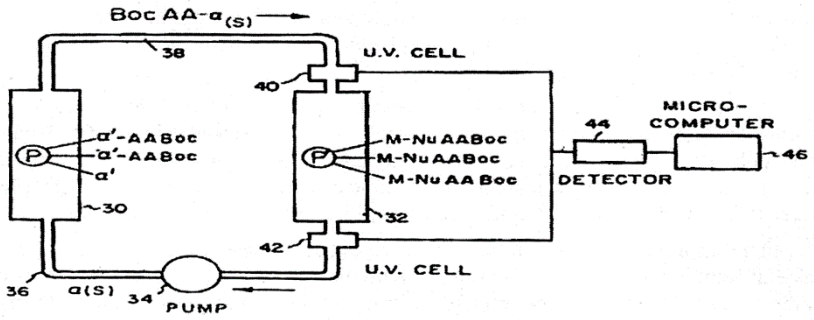


Fig.-3

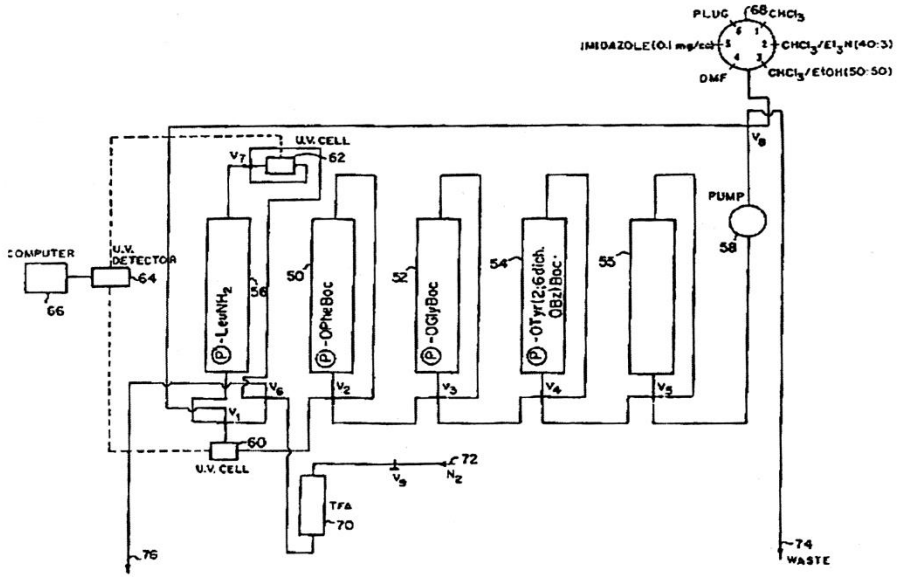


Fig.-4

In the present process, however, B is bound by a chemical bond to a reactive polymer .circle.P', usually by means of a linking moiety L, and A is bound by a chemical bond to a reactive polymer .circle.P by means of a linking moiety α'.

Intermediate reactant a, capable of reacting with .circle.P --α'--A to form α--A, is fed to the polymer on which α'--A is bound (the first column) to form the intermediate compound α-A which is then circulated to the polymer on which B is bound (the second column) where it reacts with .circle.P' --L--B to form .circle.P' --L--B--A and the original intermediate reactant a. The regenerated original a is then circulated back to the first column to react with other .circle.P --α'--A groups of the polymer and thus continue the procedure until the reaction is completed and either the first column is substantially depleted or the second column is substantially loaded.

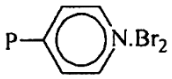
An apparatus for carrying out such a process is illustrated in Fig. 1. In this apparatus the first polymer-supported reactive species (.circle.P --α'--A) is packed into column 10 and the second polymer-supported reactive species (circle.P' --L--B) is packed into column 12. A pump 14 causes the solvent containing the intermediate compounds α and α--A to circulate between the columns 10 and 12 through tubing 16, 18 in the direction of the arrows.

A first sensor 20 is disposed at the entrance to column 12 and a second sensor is disposed at the exit from column 12. These sensors measure the chemical or physical properties of the solution passing there through. Sensors 20 and 22 provide their respective outputs to detector 24 which compares the outputs. When the outputs from sensors 20 and 22 are substantially the same, this indicates that no further reaction is taking place in column 12 and thus the reaction in column 12 has been completed.

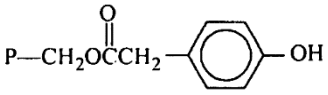
For carrying out the process Of the present invention the reactable polymers .circle.P and .circle.P' may be the same or different and may comprise any chemically modifiable polymer on which an α' or a B or L moiety, respectively, are attachable. Such polymeric support materials are well known in the art, as for example eventually, as shown in Fig. 3, the polymeric acceptor in saturated with amino acid and no further reaction will take place therein.

III. EXAMPLE

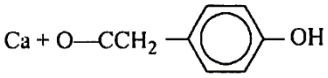
As the first polymer, ##STR2## groups may be formed from 2-4% crosslinked polyvinylpyridine. For the second polymer, ##STR3## may be prepared by mixing one equivalent of ##STR4## with 1 equivalent of .circle.P' --CH_2C1 (Merrifield polymer) in DMF/methanol (1:1) at 50°C. for 6 hours. .circle. P' is 2% crosslinked polystyrene. The first polymer is placed into a first column and the second polymer into a second column. In a water solvent, ##STRS## is circulated to the first column. After reacting with the polymer in the first column, ##STR6## is formed which then circulates to the second column. Upon reaction with the polymer in the second column, ##STR7## is formed while at the same time regenerating the ##STR8## for recirculation to the first column. The cycle is then repeated, all at ambient temperature and pressure. Ultraviolet sensors placed at the entrance and exit of the second column measure the relative presence of ##STR9## in the solvent. When the concentration of this reagent at the entrance to the column is the same as that at the exit, the second column is fully loaded and the circulation stopped.



groups may be formed from 2-4% crosslinked polyvinvinylidine according to the methods



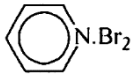
may be prepared by mixing one equivalent of



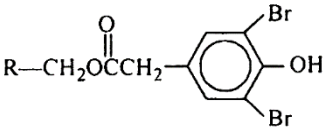
one equivalent of (P')–CH_2Cl (Merrifield polymer) ... DMF/methanol (1 : 1) at 50°C, for 6 hours. (P') is 2% crosslinked poystyrene.

The first polymer is placed into a first column and the second polymer into a second column. In a water solvent.

is circulated to the first column. After reacting with the polymer in the first column,



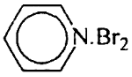
is formed which then circulates to the second column. Upon reaction with the polymer in the second column,



is formed while at the same time regenerating the

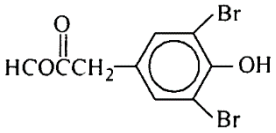
for recirculation to the first column.

The cycle is then repeated, all at ambient temperature and pressure. Ultraviolet sensors placed at the entrance and exit of the second column measure the relative pressure of



in the solvent. When the concentration of this reagent at the entrance to the column is the same as that at the exit, the second column is fully loaded and then circulation stopped.

The end product,



is then cleaved from the polymer by alkaline hyrolysis.

IV. CONCLUSION

The present invention relates to a process and apparatus for effecting chemical reactions. The process and apparatus are based on the synthesis of chemical compounds by means of certain reactive species, which are transferred from a solid polymeric support to another polymeric support. This novel process and apparatus for carrying out chemical reactions is of very versatile applicability and can be used for the selective and high yield synthesis of various types of compounds with self-monitoring.

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