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Combinatorial chemistry and its application - a review

AK Mishra[1*], A Gupta[1], AK Singh[2], P Bansal[3], S Kumar[1], V Gupta[1], BM Goyal[1]
[1] *National Institute of Ayurvedic Pharmaceutical Research, CCRAS, Patiala, India*
[2] *National Botanical Research Institute, Rana Pratap Marg, Lucknow, India*
[3] *Baba Farid University of Health Sciences, Faridkot, India*

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ABSTRACT

The use of combinatorial chemistry techniques has been explored as an alternative to conventional approaches for the synthesis of compounds in the drug discovery process. This technique is the starting point for the development of synthesis concepts that were intended to cover and explore the chemical space without having to prepare every individual compound. Combinatorial Chemistry technologies were developed in response to the increased screening capacities that are available when drug discovery changed its screening paradigm from a pharmacology-based approach to target oriented lead finding. This article will illustrate technique used in combinatorial chemistry, some of the advances made in recent years and their application in the synthesis of different peptides, oligosaccharides and other molecules.

Keywords: Combinatorial Chemistry, synthesis, solid phase, solution phase

INTRODUCTION

Combinatorial Chemistry is a technology for synthesizing and characterizing collections of compounds and screening them for useful properties—was conceived about 20 years ago. Initially, the field focused primarily on the synthesis of peptide and oligonucleotide libraries In the 1990s, the focus of the field changed predominantly to the synthesis of small, drug like Organic compounds. And many pharmaceutical companies and biotechnology firms now use it in their drug discovery efforts.(1) The drug discovery process became a highly parallel one, in which hundreds or even thousands of structures could be synthesized at one time. Sometime high throughput screening (HTS) has been performed for their in vitro assays, running assays in 96 well microtiter plates and by using laboratory robotics for pipetting and analysis.(2, 3)

Researchers continue to find ways to further enhance the capabilities of combinatorial chemistry, including these developments: A growing trend toward the synthesis of complex natural-product-like libraries, including the carbohydrate-based libraries, An increased focus on "phase trafficking" techniques are used for integrating synthesis with purification, Novel strategies for purification and analysis, such as the combinatorial use of supercritical fluid chromatography And the application of combinatorial chemistry to new targets, such as nuclear receptors.(1) The goal of combinatorial chemistry able to synthesis, purify, chemically analyze, and biologically test all the structures in the library, using as few synthetic experiments as possible.(2) Combinatorial chemistry was first applied to the synthesis of peptides. In 1963 Merrifield introduced the efficient synthesis of peptides on a solid supports or resin. Combinatorial chemistry is of two types: first is solid phase combinatorial chemistry and second is solution phase combinatorial chemistry. (2, 4)

SOLID PHASE COMBINATORIAL CHEMISTRY

In solid phase combinatorial chemistry, reagents or products are attached to solid supports such as polystyrene beads—is the most traditional form of phase trafficking. In solid-phase organic synthesis, it's easy to purify products by filtration, it's possible to do mix-and-split synthesis (a technique used to make very large libraries), excess reagents can be used to drive reactions to completion, and syntheses can be automated easily.(1) Solid phase chemistry has some advantages over the solution-phase. First, in solid-phase synthesis, large excesses of reagents can be used to drive reactions to completion; these excess reagents can then be removed at the end of the reactions by filtration and washing. Second, because of easy separation of reagents and products, solid-phase chemistry can be automated more easily than solution chemistry. Separation of compounds bound to the solid support from those in solution is accomplished by simple filtration. (4)

Solid support used in Solid phase synthesis (5, 6, 7)

Most solid state combinatorial chemistry is conducted by using polymer beads ranging from 10 to 750 µm in diameter. The solid support must have the following characteristics for an efficient solid-phase synthesis:
1) Physical stability and of the right dimensions to allow for liquid handling and filtration;

2) Chemical inertness to all reagents involved in the synthesis;
3) An ability to swell while under reaction conditions to allow permeation of solvents and reagents to the reactive sites within the resin;
4) Derivatization with functional groups to allow for the covalent attachment of an appropriate linker or first monomeric unit. (8)

The compounds to be synthesized are not attached directly to the polymer molecules. They are usually attached by using a linker moiety that enables attachment in a way that can be easily reversed without destroying the molecule that is being synthesized and allow some room for rotational freedom of the molecules attach to the polymer.
Types of solid that are used:

Polystyrene resins in this Polystyrene is cross linked with divinyl benzene (about 1% crosslinking).polystyrene resin are suitable for nonpolar solvents.

Tenta Gel resins Polystyrene in which some of the phenyl groups have polyethylene glycol (PEG) groups attached in the para position. The free OH

***Corresponding author.**
AK Mishra
National Institute of Ayurvedic Pharmaceutical Research, CCRAS, Patiala, India
Tel.: + 91-09023467630, 09023468460
E-mail:: akhileshmishra2010@gmail.com,abhibbd2006@gmail.com

groups of the PEG allow the attachment of compounds to be synthesized. PEG containing resins are suitable for use in polar solvents.

Polyacrylamide resins like super blue these resin swell better in polar solvent, since the contain amide bonds, more closely resemble biological materials.

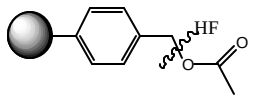
Glass and ceramic beads these type of solid supports are used when high temperature and high pressure reaction are carried out. (2)

Linkers used in solid phase synthesis (2, 9-14)

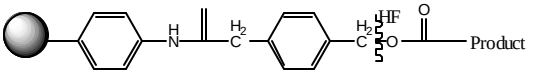
To support the attachment of a synthetic target, the polymer is usually modified by equipping it with a linker. Linker must be stable under the reaction conditions, but they must be susceptible to a cleavage. Some specialized linker have been developed to meet particular reaction or product conditions this type of linker is known as traceless linkers, it can be cleaved from the resin with no residual functionality left. This type of linkers allows the attachment of aryl and alkyl products that do not have OH or NH functionality example of these linker include silyl group (-Si(CH3)2) that is sensitive to acid and can be cleaved to give unsubstituted phenyl or alkyl product.

A new class of linkers was developed known as safety-catch linkers which is inert to synthetic condition and chemically transformed to allow final liberation of the product from the resin. Now a ultraviolet light sensitive protecting groups are used, like affymax group is used in the synthesis of carboxylic acid and carboxamide products. Some groups have used linkers that can only be cleaved by enzymes. (9-10)A novel linker possessing selenocyanate and masked carboxylic acid was developed for the solid-phase synthesis of dehydropeptides. This linker was used to demonstrate the synthesis of the model compound of RGD-conjugated dehydropeptide. (11)

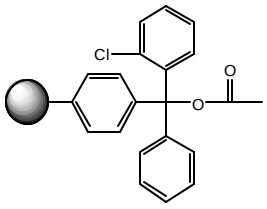
Oxabicyclo[2.2.1] norbornenes constitute a convenient and readily cleaved linker for solid-phase organic synthesis. A simple and inexpensive furfuryl-substituted resin has been shown to capture and release maleimide dienophiles under conditions compatible with intermediate synthetic steps. (12) A new linker based on a chroman system is developed for the side-chain anchoring of Arg and other guanidine-containing molecules. The system is compatible with the Fmoc/tBu solid-phase strategy, because the release of the final product is achieved by treatment with TFA in the presence of scavengers. (13-14)



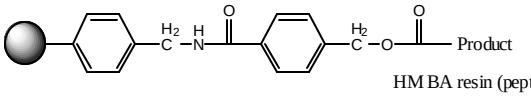
Merrifield resin (peptide products)



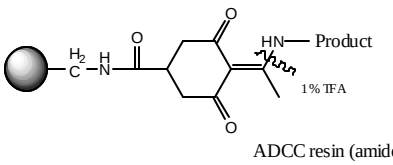
P AM resin (peptide or carboxylic acid products)



Trityl resin (carboxylic acid products)



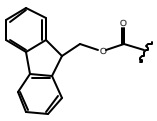
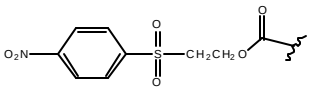
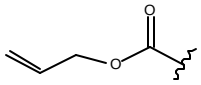
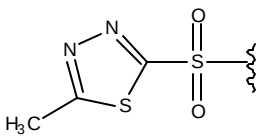
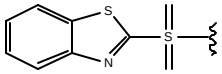
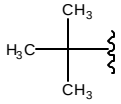
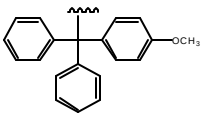
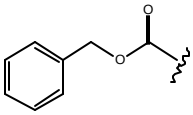
HM BA resin (peptide products)



ADCC resin (amide products)

Common protecting groups used in solid phase synthesis and their cleavage methods (4, 15-16)

Primary function of protecting group is to protect the portion of the molecule that is not covalently bound to the resin must be protected to avoid subsequent[3] polymerization of excess monomers in solution nonreactive side of linkers. The protecting group must be stable to the reaction conditions of each coupling. After coupling is performed, the protecting group is removed to expose a new reactive site and synthesis continues in a repetitive fashion Cleavage conditions are dictated by the linker used.

Protecting Group	Structure	Cleavage Method
N^a-Protecting Groups		
Fluorenylmethoxycarbonyl (Fmoc)		Base-catalyzed (20% Piperidine in DMF)
2-(4- nitrophenylsulfonyl) ethoxycarbonyl (Nsc)		Base catalyzed (20% piperidine in DMF
Allyloxycarbonyl (Alloc)		Hydrogenolysis (Pd/C; ethanol)
5-Methyl-1,3,4 thiadiazole-2- sulfonyl (Ths)		Zn-Acetic Acid Al-Hg/THF/H_2O
Benzothiazole-2- sulfonyl (Bts)		Zn-Acetic Acid Al-Hg/THF/H2O, Na2S2O4
Side-Chain Protecting Groups		
t-Butyl		Acidolysis (TFA)
Dimethoxytrityl (Dmt)		Acidolysis (Weak Acid)
Benzyloxycarbonyl (Z)		Catalytic Hydrogenation Acidolysis

Application of solid phase synthesis

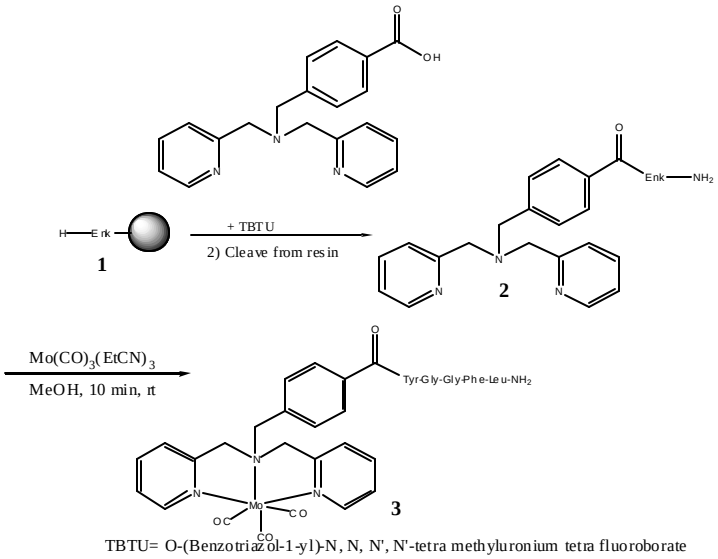
1. **Solid-Phase Synthesis of Peptide –Metal-Complex Conjugates (17)**

Solid-phase synthesis of inorganic complexes was established by

Heinze, Metzler-Nolte, Reedijk and others.(18) Coordination and organometallic chemistry on solid-phase were typically studied in the context of catalyst performance.(19) Recently, solid-phase synthesis using insoluble resins as solid support was used to synthesize metal complexes based on peptide backbone ligands. These coordination compounds find applications in biochemistry as well as in medicinal chemistry. Resin-bound chelates were prepared in such a manner that upon the addition of suitable metal salts the target metal complexes were selectively released from the resin and used.

a) Synthesis of Bis(2-picolyl)amine (bpa) molybdenum conjugate

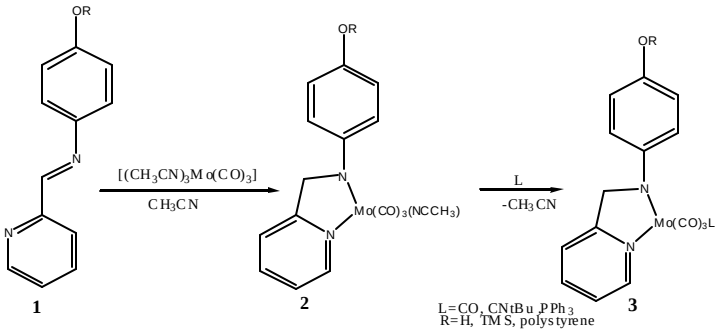
In case when the attachment of a metal complex to the peptide on the solid support is not desirable, e.g. with radioactive metal isotopes, an innocent anchoring group can be attached to the peptide during solid-phase synthesis. The ligand–peptide conjugate is then cleaved from the resin, purified and the metal label is only added in solution immediately prior to use of the bioconjugate. (20)



TBTU= O-(Benzotriazol-1-yl)-N, N, N', N'-tetra methyluronium tetra fluoroborate

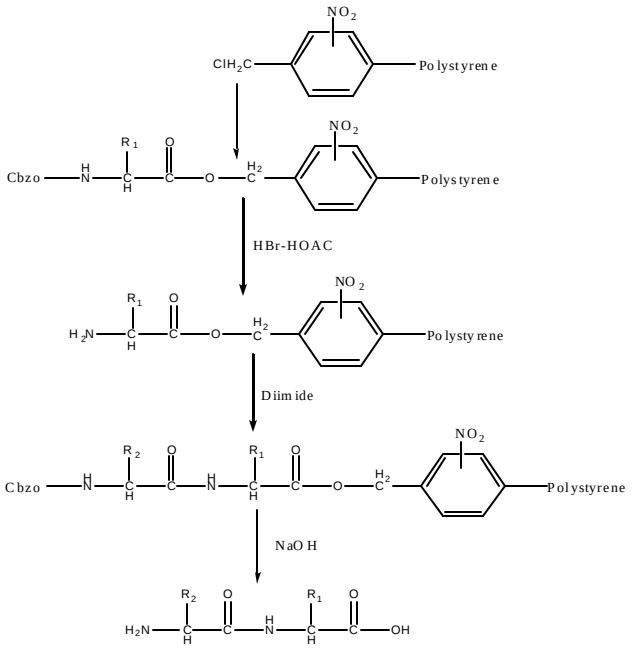
b) Bidentate schiff base metal conjugates (21-22)

A solid-phase synthesis approach for molybdenum carbonyl complexes was developed by Heinze . neither peptide coupling nor metallated amino acids are used, because it illustrates that complex organometallic transformations are possible on solid support. A specific resin and linker system allows coordination under solid-phase reaction conditions and the cleavage of the metal complex from the solid support. Bidentate Schiff base **1** was used as the ligand. The phenolic hydroxyl group allows the attachment to the solid support. A silyl ether based linker was chosen due to its stability under basic and acidic conditions and the possibility to cleave with fluoride ions, which are expected to be unreactive towards most metal complexes. In solution high temperature and rather harsh oxidative reaction conditions are necessary to synthesize the desired tricarbonyl compounds. Such harsh conditions have to be avoided in solid-phase chemistry with polystyrene resins as the molybdenum precursors can react with the aromatic residues of the support. Heinze and co-workers used $[(CH_3CN)_3Mo(CO)_3]$ as a $Mo(CO)_3$ source and under mild reaction conditions the intensely blue coloured complexes **2** and **3** formed rapidly and having excellent yields. However, acetonitrile, a rather poor solvent for resin swelling, had to be used in a mixture with toluene. The cleavage was performed with tetra-*n*-butylammonium fluoride in dichloromethane and resulted in deeply coloured solutions of the deprotonated complexes.



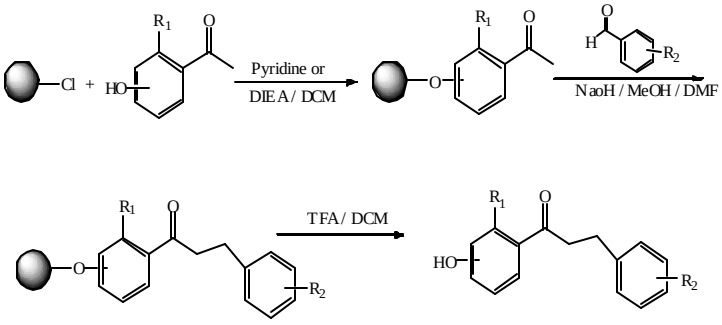
2. Synthesis of a Tetra-peptide (23)

A new approach to the chemical synthesis of polypeptides was investigated.It involved the stepwise addition of protected amino acids to a growing peptide chain which was bound by a covalent bond to a solid resin particle.This provided a procedure whereby reagents and by-products were removed by filtration, and the recrystallization of intermediates was eliminated. The advantages of the new method were speed and simplicity of operation.The feasibility of the idea was demonstrated by the synthesis of the model tetrapeptide L-leucyl-L-alanylglycyl-L-valine. To provide a point of attachment for the peptide the polystyrene resin was partially chloromethylated.The product was then nitrated or brominated.The resulting substituted chloromethyl polystyrene was treated with the triethylammonium salt of the first protected amino acid in the proposed peptide chain to give a substitutedbenzyl ester linkage. This was the stable covalent bond which held the growing peptide chain in the solid phase on the supporting resin. Protecting group which was used throughout the syntheses to be reported was the carbobenzoxy (cbzo) group.It was selected because it could be removed readily andcompletely by hydrogen bromide in glacial acetic acid stituted carbobenzoxy-L-valyl polymer even in 10% HBr-acetic acid there was also considerable loss of ester. After nitration the rate of removal of carbobenzoxy was decreased, but the loss of ester was reduced to a very small level.With 30% HBr the carbobenzoxy group (cbzo) was removed in **2** to **4** hr., while the ester cleavage remained at a low level for at least **6** hr.



3. Solid Phase Synthesis of Chalcones by Claisen-Schmidt Condensations (24)

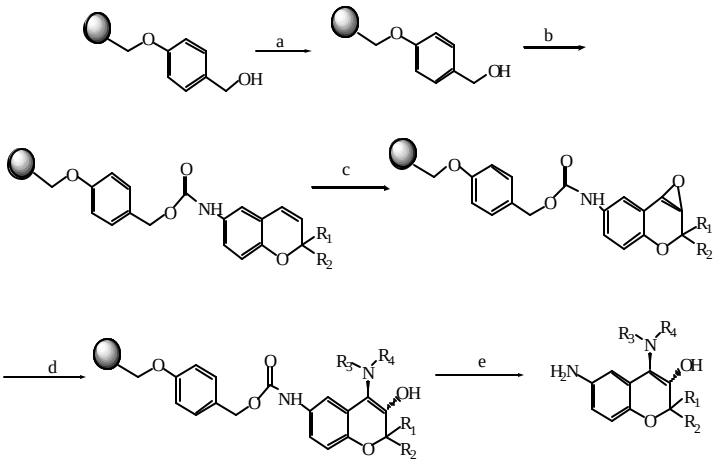
In order to accelerate the development of relatively inexpensive antimalarials that are effective against chloroquine-resistant strains of Plasmodium falciparum, a methodology for the solid phase synthesis of chalcone (l, 3-diphenyl-2-propen-l-one) analogues reasonably having high yields and purity. In a manual peptide synthesis vessel, a mixture of 3- or 4-hydroxyacetophenone or hydroxybenzaldehyde (5 to l0 eq.), pyridine or diisopropyl ethylamine (2 eq.) and 2-chlorotritylchloride resin (l00 mg, l.l-l.6 mmol/g) in anhydrous dichloromethane (3 mL) was shaken for l h at room temperature. Resin was washed with DMF (3x), MeOH (2x) and DCM (3x) and dried in vaccum. The resin-attached aldehydes (l eq.) or methylketones (l eq.) were condensed with either substituted methylketones (l0 eq.) or substituted aldehydes (l0 eq.) with NaOH (0.1 eq.) in l0% MeOH-DMF (3 mL total) at room temperature for 24 h. Resins were washed in the same sequence as the first step described above. The product was cleaved with TFA/DCM at room temperature for 20 min. Determination of product purity is done by HPLC.



-Cl : 2-chlorotrityl chloride resin; R1=H, CH3; R2=H, CH3, CH3O, F, Cl, Br, or fuzed heterocycles

4. Synthesis of Benzopyran Derivatives Using Two-Phase Solvents system (25)

Solid-phase organic synthesis has emerged as a powerful technique in generating combinatorial libraries of small organic molecules which is useful for drug discovery. Heterocyclic compounds provide scaffolds on which pharmacophores can be arranged to yield potent and selective drugs. A variety of heterocycles have been synthesized on solid support. A successful application of the epoxides **4** to generate the 3-hydroxy-4-amino substituted benzopyran library. We selected the Wang resin **1** as a polymer support, the hydroxy group of the Wang resin is useful in the introduction of 6-amino-chromenes **6** through the carbamate linker which also serves as an efficient protection group for the amino group against the subsequent oxidation and alkylation reactions. The benzopyran derivatives **6** were finally liberated from the resin by trifluoroacetic acid (TFA). In the first step, the 4-nitrophenyl carbonate resin **2** was prepared by adding pyridine in CH2Cl2 to the Wang resin **1** in the presence of p-nitrophenyl chloroformate in CH2Cl2. The reaction of carbonate resin **2** with 6-amino-2,2-dimethyl chromene and N-diisopropylethylamine (DIPEA) in N, N dimethylacetamide (DMA) afforded the carbamate resin **3** and the progress of the reaction was verified by the complete disappearance of the carbonate peak at 1760 cm-1 in the IR. it was found that the two-phase solvent system comprised of chloroform and saturated aqueous NaHCO3 was quite satisfactory. Under this condition the desired epoxide resin **was** obtained in good yield. We assumed that the success of this reaction was due to the basic aqueous solution's ability to remove excess m-chlorobenzoic acid quite effectively. The hydroxyl compounds **6** can also be used for further combination with acylating agents to preparing diverse chemical libraries for biological evaluation.



(a) p-nitrophenyl chloroformate, pyridine, CH_2Cl_2; (b) 6-amino-2,2-dimethyl chromene 7, DIPEA, DMA; (c) m-CPBA, $CHCl_3$: sat. aqueous $NaHCO_3$ (9 : 1); (d) 2 equiv. $Mg(ClO_4)_2$, 4 equiv. R_3R_4NH, CH_3CN; (e) TFA : CH_2Cl_2 (1 : 3), 4, 5, and 6 are racemates

5. Synthesis of luteinizing hormone releasing hormone analogues using 9- fluorenyl-methyloxycarbonyl amino acid (26)

Synthesis of the hypothalamic hormone, luteinizing hormone releasing hormone (LHRH) and its agonists and antagonists by using acid labile protecting groups like Boc, Z, etc., for a-amino or side-chain protection generally involves final treatment with anhydrous liquid hydrogen fluoride leading to contamination of the final product with closely related impurities thereby necessitating extensive purificaiton. In solid phase synthesis (SPS) of peptides, use of base labile 9- fluorenylmethyloxycarbonyl (Fmoc) group for Na-protection would allow milder conditions to be employed during the synthesis in addition to the requirement of minimal side-chain protection and this strategy was followed for the synthesis of LHRH analogues. The purity of the final peptides was demonstrated by paper chromatography on Whatman No. 1 chromatography paper strips by ascending method by using the following solvent systems:

A. *n*-BuOH-HOAc-H_2O (4:5:5, upper phase, v/v)

B. *n*-BuOH-HOAc-H_2O-pyridine (30:6:24:20, v/v)

Fmoc_Gly + $HOCH_2$-C_6H_4-OCH_2-C_6H_4-Resin

↓ DCC and p-dimethylaminopyridine

Fmoc-Gly-OCH_2-C_6H_4-OCH_2-C_6H_4-Resin

↓ 1) 60% Et_2NH in DMF, 180 min
2) coupling with Fmoc-amino acid active esters (3 equiv.) in the presence of 1-hydroxybenzotriazole (HOBt) (1 equiv.) in DMF

Glu-His-Trp-Ser-Tyr-D-Hpg-Leu-Arg(NO_2)-Pro-Gly-$OCH_2C_6H_4OCH_2C_6H_4$ Resin

↓ NH_3CH_3OH

Glu-His-Trp-Ser-Tyr-D-Hpg-Leu-Arg(NO_2)-Pro-Gly-NH_2

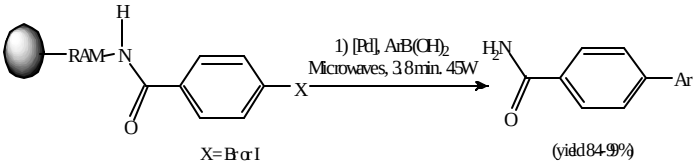
↓ 1) pd black/85% HCOOH at room temperature
2) CM Sephadex C-25
3) Sephadex G-25
4) Lyophilisation

Glu-His-Trp-Ser-Tyr-D-Hpg-Leu-Arg-Pro-Gly-NH_2 ·3HOAc

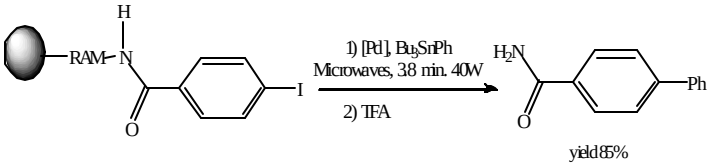
6. Microwave–assisted combinatorial synthesis (27-30)

The combination of microwave power to solid phase synthesis is quite logical. Rate accelerations and high loadings for several solid-phase protocols have been reported with reaction time being reduced in some cases from hours to a few minutes. The combination of solid phase synthesis and microwave heating is receiving attention and this combination has enormous potential for better results Larhard *et al.* have demonstrated that highly useful Suzuki and Stille reactions could be conducted under flash-heating conditions using a single mode cavity and would afford better yields. They reported microwave-assisted palladium-catalyzed coupling of aryl and heteroaryl boronic acids with iodo- and bromo-substituted benzoic acids, anchored to Tenta Gels RAM, provided high isolated yields of coupled products after a reaction time of 3.8 min. Suzuki and Stille reactions worked readily on a polymeric support consisting of a benzoic acid linked to Rinkamide on polyethylene glycol (PEG) grafted polystyrene (TentaGel). The polymer was found to be stable under these harsh conditions.

(a)



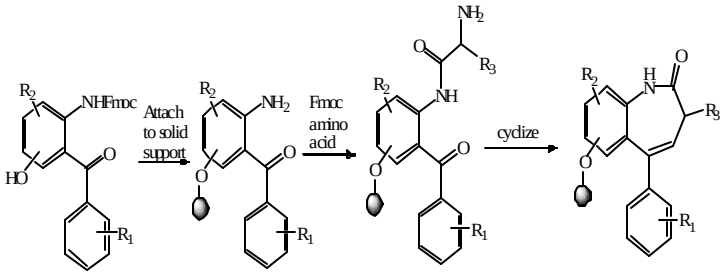
(b)



(a) Suzuki coupling on Solid-Phase Assisted by Microwave Inradation. (b) Microwave assisted stille reaction on polymer tethered 4-iodobenzoic acid

7. Synthesis of 1, 4 benzodiazepines (2, 3)

The choice of benzodiazepines was inspired because of the medicinal importance of these materials and their resemblance to peptides. Here the library was constructed by a combination of three reactants. In the synthesis 1, 4 benzodiazepines Fmoc is used as a common protecting group and detachment of solid support is done by tetrafluoroacetic acid.

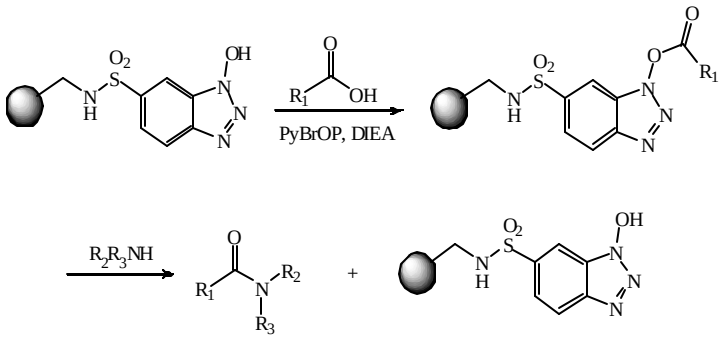


SOLUTION PHASE COMBINATORIAL CHEMISTRY

Most ordinary synthetic chemistry takes place in solution phase. The use of solution phase techniques has been explored as an alternative to solid-phase chemistry approaches for the preparation of arrays of compounds in the drug discovery process. Solution-phase work is free from some of the constraints of solid-phase approaches but has disadvantages with respect to purification. In solution phase synthesis we use soluble polymer as support for the product. PEG is a common vehicle which is used in solution phase synthesis it can be liquid or solid at room temperature and show varying degrees of solubility in aqueous and organic solvent. By converting one OH group of PEG to methyl ether (MeO-PEG-OH) it is possible to attached a carboxylic acid to the free OH and use in solution phase combinatorial synthesis. Another common support which is used in solution phase synthesis is liquid Teflon consisting mainly of long chain of (-CF_2-) groups attached to a silicon atom. When these phases are used as a soluble support for synthesis the resulting product can be easily separated from any organic solvent. (2, 31)

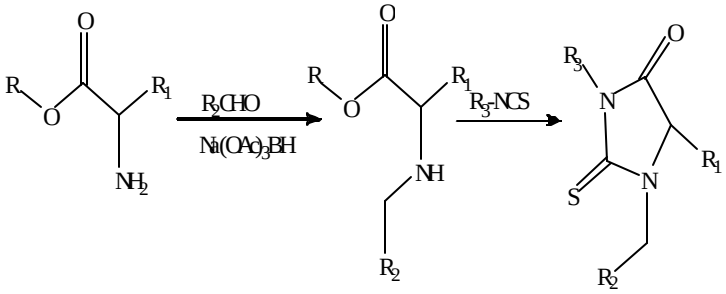
1.Synthesis of Polymer By Solution Phase Combinatorial Chemistry (31-33)

Tartar and co-workers reported the synthesis of polymer supported 1-hydroxybenzotriazole. Reaction of the reagent with a carboxylic acid in the presence of an activating agent afforded the polymer bound activated ester which was reacted with amines to liberate the amide in solution. Supported electrophilic, nucleophilic or ionic reagents used to remove impurities from solution have been termed scavenger reagents; polymer supported quenching reagents (PSQ) or complementary molecular reactivity/ molecular recognition polymer (CMR/R polymer). Use of such reagents provides a versatile counterpart to the approach. Booth and Hodges utilised a high loading amine resin derived from chloromethylpolystyrene and tris(2-aminoethyl)amine in the preparation of ureas, thioureas, sulphonamides and amides.



2. Synthesis of Thiohydantoins (31, 34)

Sim and Ganesan developed a one-pot three component synthesis of thiohydantoins using the reductive amination of amino esters with aromatic aldehydes and sodium triacetoxyborohydride followed by the reaction with an isocyanate in the presence of triethylamine. The thiohydantions were isolated by an aqueous work-up protocol which incorporated the addition of glycine to convert unreacted reagents into water soluble materials. The methodology was used in the preparation of an array of 600 discrete compounds.



3. Solution Phase Synthesis of Biologically Important Oligosaccharides

We departed from the traditional goal of oligosaccharide total synthesis striving for maximum convergency, and followed a linear synthesis approach based on monosaccharide building blocks. Using this method similar to that practiced for peptides and oligonucleotides we assembled several complex structures.

a)Synthesis of High Mannose Structures of HIV gp120 (35)

We completed the synthesis of a series of highly branched mannosides found on gp120 of HIV. Two different trisaccharides, a hexa-, and a nonasaccharide were prepared in conjugatable form. These structures were used to investigate the interaction of cyanovirin-N, a highly potent topical anti-HIV agent, with gp120. In collaboration with Barry O'Keefe (NCI) and Angela Gronenborn (NIH) isothermal calorimetry and high-field NMR were used to establish the minimal binding sequence and to map the binding site on the protein.

b)Synthesis of Oligosaccharide Antigens Involved in Cancer and Bacterial Infections (36)

Cell surface carbohydrates act as biological markers for various tumors and are involved in bacterial and parasitic infections. Specific carbohydrate structures are found on particular cell populations and may be used to induce a specific immune response. These complex structures require reliable methodologies for their assembly. The Lewis antigens, a class of glycosphingolipids, are essential for cellular adhesion and recognition. In addition to their role in normal cellular adhesion processes such as the inflammatory response they have been implicated in many types of cancer and bacterial infections. We developed new synthetic routes for the modular assembly of the Lewis antigens as demonstrated on the example of H-type II that lend themselves to automation. Other tumor-associated antigens including Gb3 have also been prepared. The oligosaccharides obtained from these syntheses are currently being attached to surfaces to enable rapid screening of carbohydrate-protein interactions.

CONCLUSION

Combinatorial chemistry continues to provide an important technique particularly to the medicinal chemist engaged in lead optimization work. combinatorial chemistry and parallel synthesis can greatly benefit by their unique features offered by new synthetic technology. These include the possibilities of high-speed parallel processing of chemical transformations in the context of library production, and the rapid optimization of reaction conditions. Among the solid and solution phase synthesis Solid-phase organic synthesis (SPOS) is the most important method for the production of combinatorial libraries because all the synthetic transformations successfully applied to solid phase and with the development of high-throughput screening, libraries are widespread in pharmaceutical and agricultural chemistry.

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