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Multicomponent Reactions and Their Libraries – a New Approach to Preparative Organic Chemistry*

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Classical chemical syntheses from n starting materials usually require sequences of at least n-1 preparation steps, including separation and purification of the intermediates. A perfect alternative for the rapid syntheses of a large variety of agrichemically and pharmaceutically relevant products are one-pot syntheses by multicomponent reactions (MCR) on the basis of isocyanides. Four to seven different types of components mixed in a reaction vessel undergo the transformation to one molecule. Due to the last irreversible step that involves the isocyanides, a stable product results in quantitative yields. Using more than one representative of each type of starting materials (*i.e.* different isocyanides, amines, *etc.*) in the same vessel, all possible combinations will lead to a molecular library with hundreds and thousands of products formed according to a given reaction scheme. The design of such syntheses and the handling of the results require adequate mathematics and computer tools.

INTRODUCTION

Conversions of three or more initial compounds into a product usually require several steps. However, in an increasing number of cases it is also possible to form the desired products from more than two different starting materials by one-pot multicomponent reactions (MCR).

Till 1959, most of the MCRs involved reversible α-aminoalkylations of nucleophile with three components, which were sometimes followed by sec-

* Dedicated to the 90th birthday of Vlado Prelog.

ondary reactions with further components to form heterocyclic products which were formaly irreversible in practice.

One of the exceptions was the Passerini reaction, a 3CR of carbonyl compounds, carboxylic acids and isocyanides. Isocyanides are the only stable organic chemical compounds with formally divalent carbon C^{II} and a not yet sufficiently explored part of organic chemistry. They had been easily accessible since 1958. Their MCRs of four and more components were introduced shortly afterwards. Nowadays, isocyanide-MCRs are an important field of preparative organic chemistry. Still new MCRs are developed, because they are of excellent use in combinatorial chemistry for building collections of different chemical compounds, the so-called molecular libraries. Huge libraries of small drug-like organic compounds are a particularly challenging area of investigation, especially in the pharmaceutical industry.

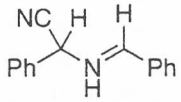
If the desired products are formed from three or more different materials, several preparative steps must be usually carried out. In each chemical step an intermediate product is isolated, purified and reacted with the next starting material, until the final product is obtained. The common multistep syntheses require a great deal of chemical work and do not have high final yields, since not all preparative steps proceed extremely well.[1]

However, in many cases, multi-step syntheses can be replaced by one-pot MCRs of many different starting materials. The MCRs have great preparative advantages: Their products can be obtained just by mixing three and more chemical compounds and proceeding without special conditions. Isocyanide-MCRs form their products practically irreversibly and have no competing reactions. Their yields are usually quantitative.

The recent development of combinatorial organic chemistry requires new mathematically oriented theories and computer tools. The formation of libraries and their transformations during secondary reactions, their isolation, their data handling and the investigation of the observed and desired properties all require new types of reasoning.

THE CLASSICAL α-AMINOALKYLATIONS BY 3CRS AND SECONDARY REACTIONS WITH MORE COMPONENTS

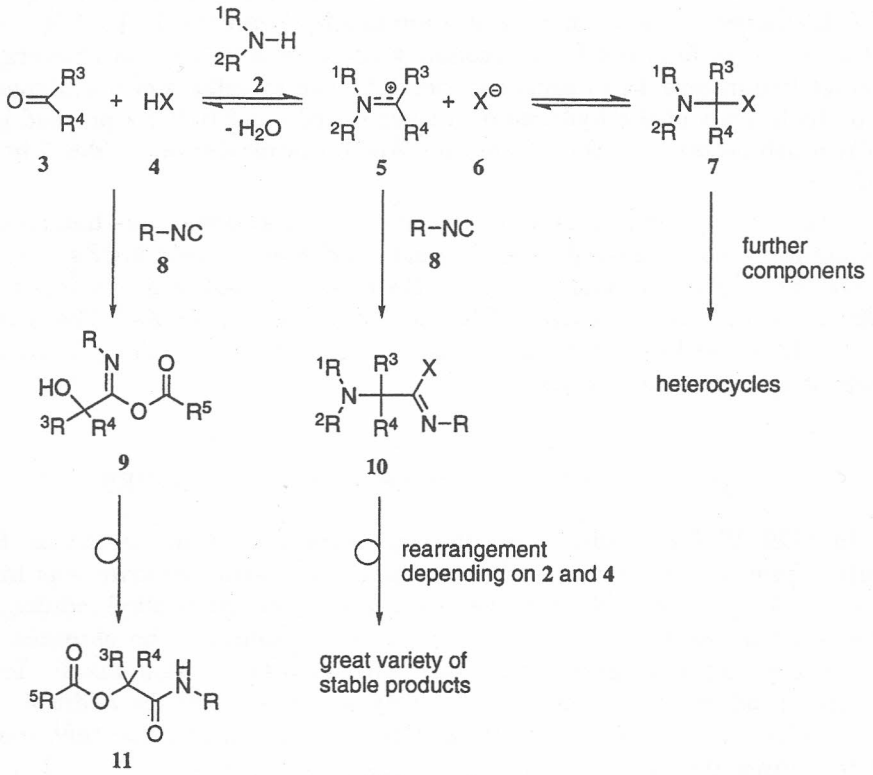
The first MCR was discovered by A. Laurent and C. F. Gerhard in 1838.[3] They realized that a compound in the oil of bitter almonds reacts with ammonia and forms the crystalline product **1**.



1

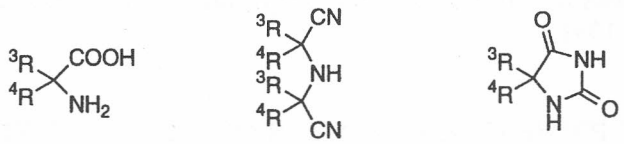
Scheme 1.

This oil contains the decisive chemical compounds, benzaldehyde **3** (R^3 = H, R^4 = C_6H_5) and hydrogen cyanide **4** (HX = HCN). The first step in this reaction with ammonia **2** (R^1 = R^2 = H) is an α-aminoalkylating 3CR, which forms the intermediate product **7**. This reacts with a second molecule of benzaldehyde to form **1**. Around 1850, this type of 3CR became one of the first name reactions, the Strecker reaction,[4] S-3CR.



Scheme 2.

Products **7** (X = CN) of the S-3CR can be converted into α-aminoacids **12**, however in most cases, besides **7**, also large amounts of the often very toxic by-products **13** are formed.



12 **13** **14**

Scheme 3.

These 3CRs correspond to α-additions of cations onto anions of weak acids or nucleophiles, and generally do not have very high yields since such 3CRs are reversible and, in addition, competitive reactions often take place.[4]

In the MCRs of four and five components, the α-aminoalkylations or analogous reactions are the first steps, whose intermediate products react with further components and form heterocyclic final products, practically irreversible. The first step of the BB-4CR, discovered in 1929 by H. Bergs and H. T. Bucherer, is the formation of α-aminoalkyl-cyanides **7** (X = CN) by S-3CRs, which is followed by a secondary reaction with CO_2 to irreversibly produce hydantoins **14** in excellent yields.[2,4] The syntheses of α-aminoacids **12** by hydrolysis of the hydantoins **14** generated *via* BB-4CRs proceed generally much better than their formation from α-aminoalkyl-cyanides **7** in the S-3CR.[4]

α-Aminoalkylations and their secondary conversions into heterocyclic compounds were developed a century ago, and these classic MCRs were reviewed by Hellmann and Opitz in their book about α-aminoalkylation (1960).[4] All of these classical MCRs can be called HO-MCRs.[1] These reactions yield either final products or intermediates that can react with further components into heterocycles.

THE EARLY CHEMISTRY OF THE ISOCYANIDES

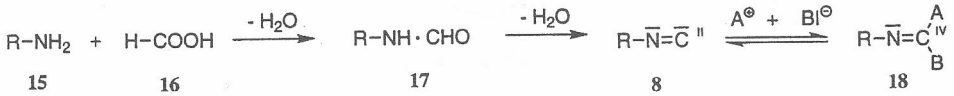
In 1859, W. Lieke[5] discovered the first formation of an isocyanide (**8**, R = allyl) from allyl iodide and silver cyanide. The term *isonitrile* was introduced by A. Gautier,[6] who produced alkyl isocyanides from alkyl iodides and silver cyanide, and simultaneously by A. W. Hoffmann,[7] who obtained isocyanides by treating primary amines with chloroform and alkali. These methods produce isocyanides in relatively low quantities. In addition, the isocyanides were not easy to isolate. However, the most important reason for the unpopularity of isocyanide chemistry is the intense »evil odour« of most isocyanides, which »taint the air in a room for days«.[8]

The chemistry of the isocyanides was not investigated very much during the first century after their discovery, except by M. Passerini.[9,10] In 1921 he discovered the one-pot reaction of carbonyl compounds **3**, carboxylic acids **4** (HX = HOOC-R^5) and isocyanides **8** to produce α-acyloxy-carbonamides **11**. This P-3CR was the first 3CR of the isocyanides, which M. Passerini investigated until 1931.

THE PRESENT PREPARATION OF THE ISOCYANIDES

Better methods of preparing isocyanides were not introduced until the late 1950s. The lack of simple preparative methods was probably the main

reason why the chemistry of isocyanides was a rather poorly researched area of organic chemistry. It was realized early on that the isocyanides are the only divalent carbon C^{II} compounds **8** in organic chemistry. All of their chemistry corresponds to conversions between the divalent and the tetravalent states C^{II} and C^{IV}, which is completely different from the rest of organic chemistry.[6,8]



Scheme 4.

A. Gautier[6,8] already had the idea to produce isocyanides **9** by dehydrating the formates of amines, by using P_2O_5 as a dehydrating agent. Due to the absence of a basic compound he was not successful, since isocyanides are quickly destroyed in acidic media. In 1956, I. Hagedorn and A. Tönjes[8,11] prepared the *O,O'*-dimethyl-protected antibiotic *Xanthocillin*. They dehydrated the corresponding bisformylamine with benzenesulfonylchloride in pyridine.

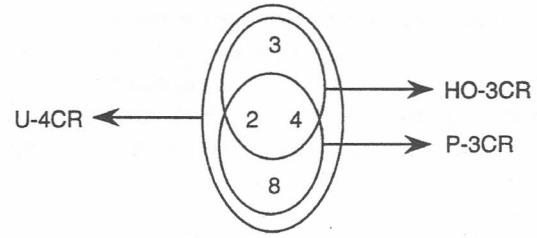
We found in 1958 that $POCl_3$ and pyridine or various tertiary amines convert *N*-alkylformamides into isocyanides quite well, but the *N*-arylformamides **17** are dehydrated better in the presence of ^{t}BuOK as a base.

Research in the field of isocyanides became rather active, and even more so when *Isonitrile Chemistry*[8] was published in 1971. Apparently, this survey had stimulated many colleagues, who began to develop some new chemistry of the isocyanides.[1] It was gradually realized that the chemistry of the isocyanides contains a wide variety of chemical reactions. In 1985, it was found that isocyanides are generally formed particularly well from formamides in the presence of di-isopropylamine with $POCl_3$ as dehydrating agent.[12] Phosgene, diphosgene,[12] and triphosgene[13] and a variety of bases are also good dehydrating reagents in the preparation of isocyanides.

The isocyanides are thus easily accessible, and their use in preparative chemistry can be carried out without the awful smell of isocyanides, since quite suitable equipment and preparative methods are now available.

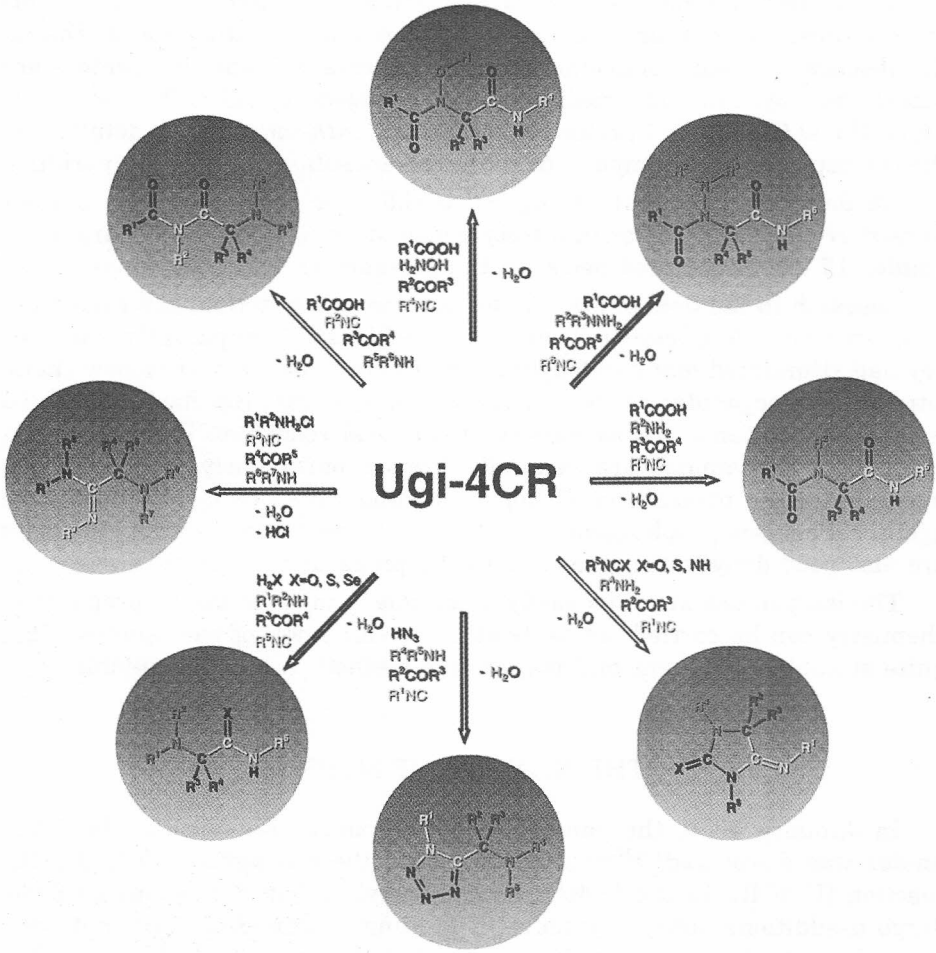
THE NEW ERA OF MCRS

In January 1959, the one-pot Four Component Reaction of the isocyanides was discovered[1,8,10,14] and since 1962 the colleagues call it the Ugi reaction (U-4CR). In the U-4CR, α-aminoalkyl cations **5** and anions **6** undergo α-additions onto isocyanides **8**, forming intermediates **10** that rearrange into stable products. This one-pot U-4CR is formally the union [15] of the HO-3CR[4] and the P-3CR[8–10] (Scheme 5).



Scheme 5.

Interestingly, the U-4CR is not just a single type of reaction. In the MCRs of the isocyanides, three and more components equilibrate, and only



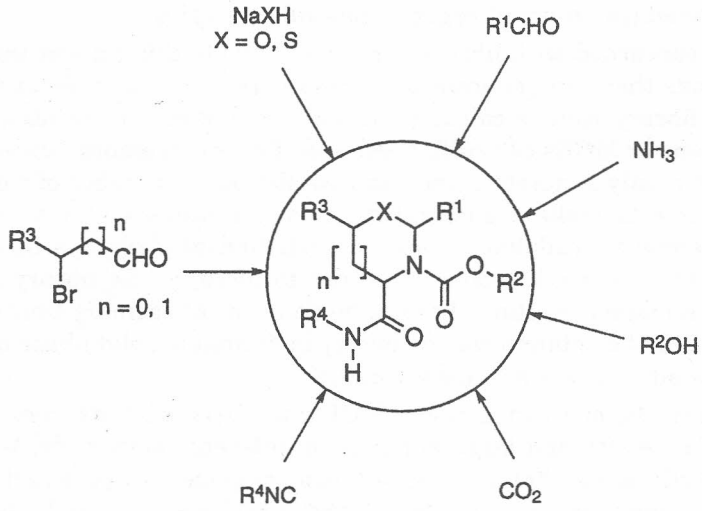
Scheme 6.

the final α-addition of cations and anions onto the C^{II} of the isocyanides is irreversible and forms intermediates **10**, where the C^{II} have been converted into C^{IV}. The great variety of different types of final U-4CRs arises from the last step of the reaction, the irreversible rearrangements of **10** into stable products.[8] The final rearrangement depends on the different types of amines **2**, acids **4** and isocyanides **8** used in U-4CR. (Scheme 6).

Early investigations of the U-4CR reactive components showed that the carboxylic acids can be replaced as a starting material by alcohols and CO_2, which form α-alkyloxycarboxylic acids. This reaction corresponds to a one-pot reaction of five compounds, the U-5CR.[1,8]

In 1967, intermediates of the U-4CR were discovered, which can react with further nucleophiles and form final products, also in quantitative yields.

In 1993, the first unions of MCRs have been carried out. The first 7CR (Scheme 7) was published, which illustrates this fundamental progress.[17]



Scheme 7.

In recent years, we developed methods to react an even greater number of different components (five to seven different chemical compounds) in a one-pot MCR with the isocyanides.[1,16,17]

The one-pot MCRs have generally great preparative advantages over the syntheses that are multi-step sequences of reactions where one or two components participate at each reaction step. The MCRs proceed particularly well if all components and intermediate products are subject to equilibria, and only in the final one or two steps of the reaction towards the product

they take place irreversibly. Therefore, the formations of heterocycles by MCRs and the MCRs of the isocyanides go to completion with good yields.[2]

It seems that this progress in preparative chemistry, in the past few years, has changed organic chemistry quite fundamentally.

THE LIBRARIES OF MCRS

Drug candidates traditionally have been made one by one in time consuming and expensive processes. A chemist in industry was normally able to synthesize 200 to 400 drug-like compounds a year. Nowadays, chemists in pharmaceutical industry accelerate the process by using combinatorial chemistry. The idea is to synthesize large numbers of compounds at a stroke according to a given scheme – the so-called molecular libraries. Mixtures of compounds in living cells serve as examples of natural molecular libraries. Over the past decade the pharmaceutical industry has investigated peptide libraries by sophisticated preparative multi-step procedures.[18] However, the focus is nowadays on small organic molecule libraries.[19]

People concerned with library syntheses have to think about the number of compounds they can generate with specific reactions and about the diversity of the library. Simple calculations suggest that only conventional multi-step reactions or MCRs can fulfil these specific requirements. Since ordinary reactions can only generate a very limited distinctive number of compounds, chemists have to make sequential multi-step syntheses. For example, the 200 commercially available carboxylic acids and alcohols can be combined to only 40 000 carboxylic esters. In order to increase the library and their diversity, secondary reactions have to be done on the primary library. Therefore, this kind of combinatorial chemistry is limited to solid phase chemistry, with all its advantages and disadvantages.

Alternatively, one can perform MCR chemistry with its very great advantage of diversity and large numbers of different compounds. With about 200 carboxylic acids, 200 amines, 200 oxo components and about 20 isocyanides available as starting materials, the U-4CR can produce huge libraries of up to 160 000 000 compounds. Even larger libraries can be generated by performing variations of the U-4CR. In this kind of chemistry, one may prefer either the solid phase or liquid phase chemistry since Ugi-MCRs are suitable for both.

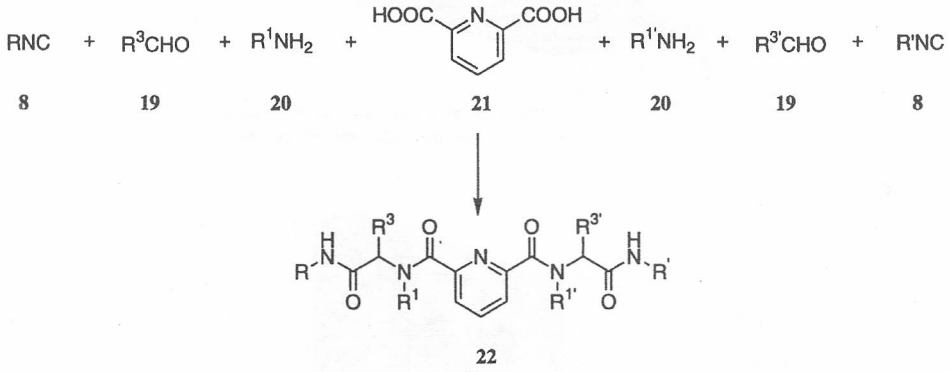
MATHEMATICS AND COMPUTER SCIENCE AS A BASIC SUPPORT FOR PREPARING MCR LIBRARIES

In order to design molecular libraries in a reasonable way, one needs different information than in the classical synthesis planning.[20,26] How many

different compounds will the library contain? How similar or different are these? Will the compounds be produced in comparable amounts carried out by an all-in-one-pot-reaction? The answers to these questions involve some mathematical and computer programming.[20] Another problem is the management of the data flood of combinatorial chemistry information which is generated.

THE SIZE OF MOLECULAR LIBRARIES

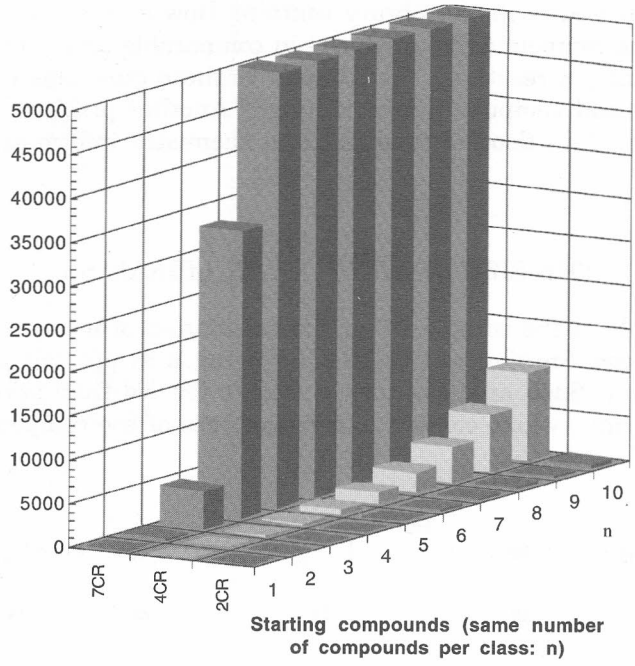
An example of the complexity of the calculation of a molecular size library is the combination of two U-4CRs using a symmetric dicarboxylic acid component. Such products turn out to be formed from seven different starting materials, which contain four basic types of the components of two U-4CRs.



Scheme 8.

In praxi the GC-spectra of the simplest version of this reaction (R = R', $R^1 = R^{1'}$, $R^2 = R^{2'}$, Scheme 8) already shows three different peaks, the *RR*-, *SR*-, *RS*-isomers. Using two components of each type in a one-pot synthesis, the GC-spectra of the product-mixture with over 100 peaks are much more difficult to analyze, because a high number of different products (expected: 272 different products) are formed with this union of two U-4CRs.

The size of such a library is determined by the number of reacting compounds. In general, for a *c*-component reaction with *c* different classes A, B, C,... (the U-4CR involves four classes: amines, aldehydes, carboxylic acids and isocyanides), the library grows linearly with the size of each class and (given equally sized classes) exponentially with the number of classes. When more than one component of the same class appears in a single reaction, the library grows much faster, *i.e.* polynomially with the size of the classes.


50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
7CR
4CR
2CR
1
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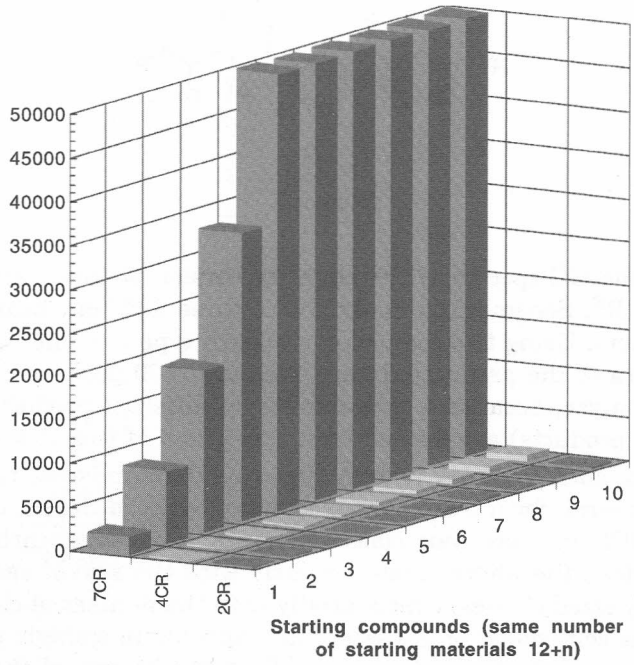
4
5
6
7
8
9
10
n
Starting compounds (same number of compounds per class: n)


50000
45000
40000
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25000
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15000
10000
5000
0
7CR
4CR
2CR
1
2
3
4
5
6
7
8
9
10
Starting compounds (same number of starting materials 12+n)

Scheme 9.

The size of such combined U-4CR-libraries is calculated as follows: The products correspond to sequences X-d-X, where d stands for the dicarboxylic rest and X is the class made up by the sequence of one representative of class A (consisting of $|A|$ amines), B (aldehydes) and C (isocyanides). Class X contains $n = |A| \cdot |B| \cdot |C|$ constitutionally different representatives. In order to handle the meso-forms of the formed molecules, sequences of the type x-d-x and x-d-y (where x is constitutionally different from y) have to be treated separately. The meso-forms exist only for the first case. All n constitutionally different sequences x-d-x correspond to three stereoisomers: *RR*, *SS*, *RS* (= *SR*). Thus each segment x-d-x corresponds to $3n$ chemically different molecules.

For each of the n possibilities of x in the sequence x-d-y, there are n–1 constitutionally different possibilities for y. Accordingly, there are $n \times (n-1)$ different sequences with x ≠ y. Because of the symmetry of the dicarboxylic acid, the compounds represented by the sequence x-d-y are equal to those represented by y-d-x, which halves the number of sequences representing constitutionally different compounds. However, each of these has its four different stereoisomers, the *RR*, *SS*, *RS*, *SR*.

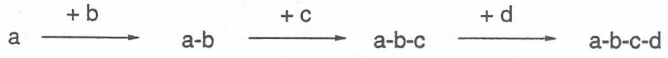
With m number of different dicarboxylic acids, there are overall $m \times (3n + 4n(n-1)/2) = m \times (2n^2 + n)$ chemically different compounds, sequences of the type X-d-X. Interestingly the number of different compounds produced from a monocarboxylic acid (and thereby only four starting materials are used per product) is only $m \times n$.

The more different classes of reagents participate and the more participants of each class appear in a single reaction, the bigger is the product variety. Scheme 9 shows from left to right the increase of the three different types of libraries (produced by union of two U-4CRs (7CR), a U-4CR and a typical 2CR like esterification). The left figure shows the increase of the libraries using the same number of compounds per class (1,1,1,1), (2,2,2,2),... whereas the right figure shows the increase varying only the size of one class (1,4,4,4), (2,4,4,4),... In each step, the same number of starting materials is used for each of the three reactions. The increase of the 2CR is apparently slower than the growth of the 4CR. Both grow linearly. However, the 7CR with four different classes grows polynomially.

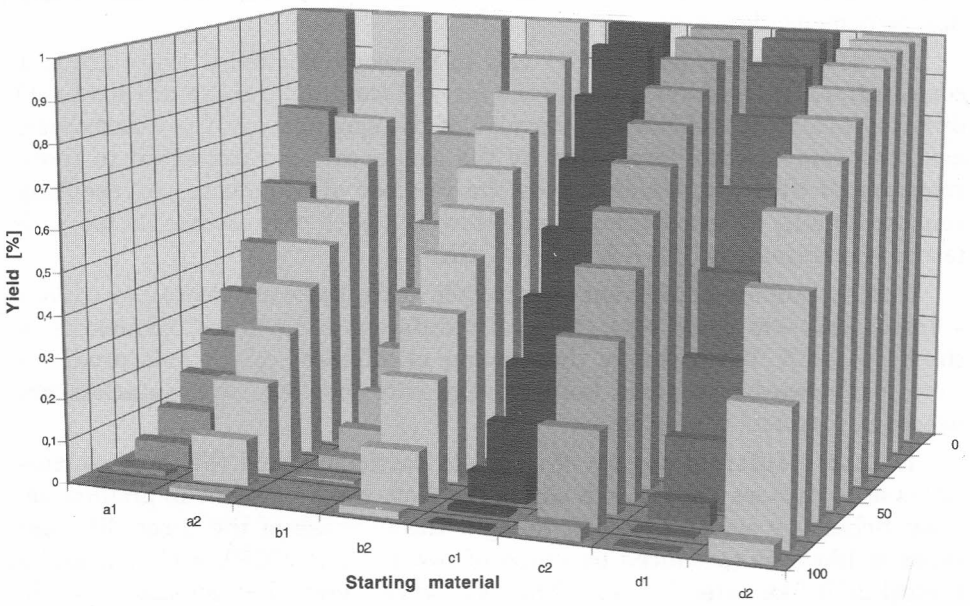
SIMULATION OF CONCURRENT MCR

Simulations of the reaction steps of MCRs help determine the amount of each product. Some simulations done for (2,2,2,2)-U-4CR, which are libraries of the U-4CR using classes A, B, C, D made up of a 'fast' (a1, b1,c1, d1) and a 'slow' representative (a2, b2, c2, d2), show very different concentrations of the products. This corresponds to the competition between the re-

action partners. The reaction is assumed to take place in the sequence shown in Scheme 10.



Scheme 10.

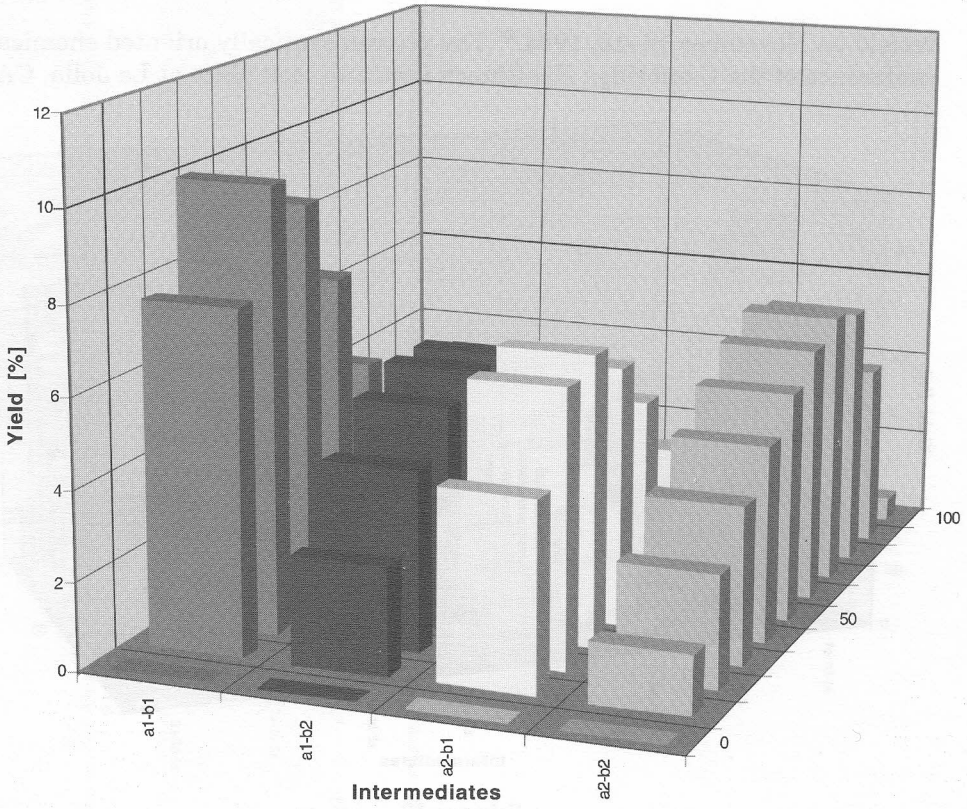


Scheme 11.

Scheme 11 shows the different reactivity of each of the two compounds as the reaction proceeds. Compounds a1, b1, c1 and d1 are consumed faster (note that the axis 'Turnover' of this scheme is in the opposite direction from those in the following schemes).

Scheme 12 shows that after the intermediates a-b are formed, they are rapidly consumed by the next reaction step. Scheme 13 indicates that the intermediates a-b-c are already formed in very different concentrations.

The final products (Scheme 14) have concentration differences of even more than 1 : 8. In order to obtain approximately equal concentrations of every product, computer programs calculate descriptions of syntheses in terms of time-dose functions.



Scheme 12.

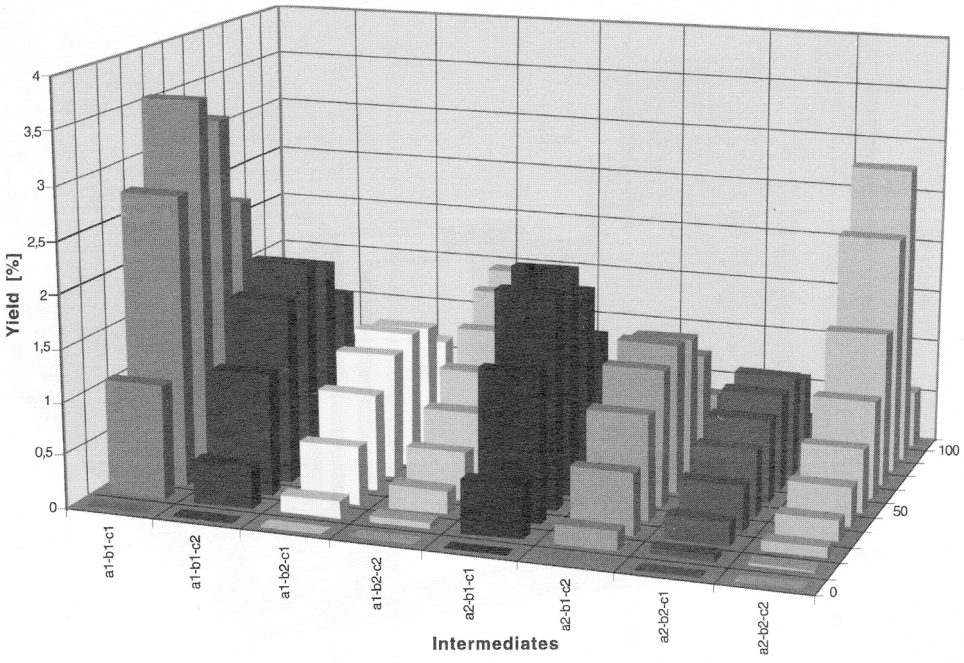
PERSPECTIVES

Via combinatorial chemistry, a fast and permanent progress in chemistry has taken place in the last few years. The research in organic chemistry, in biology and in pharmacy has changed quite profoundly. This includes the spheres of new methods in the preparative, technological and analytical chemistry.

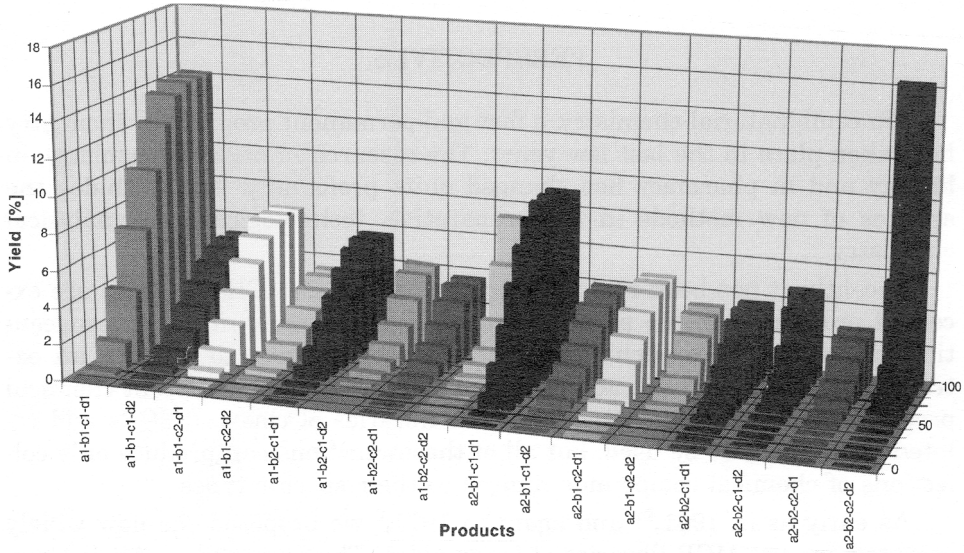
Recently, it has been realized that the one-pot U-MCRs libraries are excellent procedures in the plant protection chemistry and in the pharmaceutical chemistry, since such reactions allow the chemist to produce an extremely wide variety of structurally and stereochemically different chemical products through one-pot reactions. The libraries of classical 3CRs and related 3CRs can also be used, but all of these reactions can produce only collections of chemical compounds limited to their specific types.

As early as in 1961,[22] and again in 1971,[8] we proposed the now widely accepted one-pot MCR libraries of isocyanides. The first modern MCR libraries were publicly mentioned by our group at the GDCh-Workshop of Bit-

terfeld on November 16–18, 1994.[20] The pharmaceutically oriented chemical conference of the Cambridge Healthtech Institute took place at La Jolla, CA,



Scheme 13.



Scheme 14.

USA, on January 23–25, 1995, and there many American and Japanese colleagues were extremely interested in our presentation.[1]

Shortly afterwards, R. W. Armstrong introduced the »Combinatorial Libraries Related to Natural Products« at the American Chemical Society Conference at Anaheim in California/USA. His new application of the old cyclohexenyl isocyanide[23] onto a solid phase to generate U-4CR libraries in order to increase library diversity was a particularly interesting development in this field.

In the meantime, many groups and companies in the USA and Europe published interesting papers on combinatorial chemistry of MCRs.[24] For example potent antitumor antibiotics,[24] thrombic inhibitors[21] and compounds against multiple drug resistance[25] could be developed.

In the preparative area of combinatorial chemistry, our goal is to increase the diversity of libraries through secondary reactions and especially the union of MCRs.[2] One can easily imagine that the combination of reactions with high diversity, like the U-4CR and the Asinger reaction A-3CR or the Mannich reaction M-3CR, can increase the number of available compounds to quasi infinity.[17]

The formation and use of such libraries can be improved and assisted by computer methodology. We have developed several types of mathematically oriented computer tools. One of these will help choose the starting material in liquid and solid libraries. Other computer tools will organize the application of organic libraries, and optimize the minimal number of experiments.

Presently, a majority of chemical companies quickly generate U-MCR libraries. Many of these companies do not apply peptide libraries any more. It is assumed that U-MCR libraries will generally remain the most convenient and widely applicable method for library generation.

It can be expected that, in the next century, the preparation of chemical products will be carried out by simpler procedures with overall higher yields and less work. Thus, more and more MCRs will be found and applied. The production of chemical compounds, their analytical procedure and the determination of their structures will become increasingly based on computer oriented automatic devices. Chemical scientists will be needed more for reasoning and designing library synthesis than in practical production.

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SAŽETAK

Višekomponentne reakcije i njihove biblioteke – novi pristup preparativnoj organskoj kemiji

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Klasične kemijske sinteze iz n vrsta polaznog materijala obično zahtijevaju barem n-1 preparativnih stupnjeva, uključujući i odjeljivanje i pročišćavanje međuprodukata. Savršena alternative za brze sinteze velikog mnoštva agrokemijski i farmaceutski važnih produkata jesu sinteze koje se provode u jednoj posudi (jednom koraku) s višekomponentnim reakcijama (MCR) na bazi izocijanida. Četiri do sedam različitih tipova reaktanata pomiješanih u reakcijskoj posudi transformiraju se u jednu molekulu. Zahvaljujući posljednjem ireverzibilnom stupnju, koji uključuje izocijanide, nastaje stabilan produkt u kvantitativnom iskorištenju. Upotrebom više od jednog predstavnika od svake vrste polaznih materijala (npr. različiti izocijanidi, amini, itd.) u istoj posudi, sve moguće kombinacije dovest će, prema danoj reakcijskoj shemi, do molekulske biblioteke sa stotinama i tisućama stvorenih produkata. Smišljanje takvih sinteza i obradba njihovih rezultata zahtijevaju odgovarajuće matematičke računalske alate.