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Dedicated to Professor Jüri Kann on the occasion of his 60th birthday

MCR XXIII. THE HIGHLY VARIABLE MULTIDISCIPLINARY PREPARATIVE AND THEORETICAL POSSIBILITIES OF THE UGI MULTICOMPONENT REACTIONS IN THE PAST, NOW, AND IN THE FUTURE

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Abstract. The organic chemistry has three types of one-pot multicomponent reactions (MCRs). These do not proceed directly but stepwise by reactions of two participating chemical compounds. All components of the MCRs of type I equilibrate, whereas in MCRs of type II most of the participating components equilibrate, but at least the final formation of the product proceeds in practice irreversibly. The MCRs of type IIA proceed without changing the number of chemical bonds and are preparations of heterocycles, whereas type IIB corresponds to an increase in the formal number of chemical bonds, and these are usually MCRs of the isocyanides. The MCRs, particularly those of type II, have great preparative advantages over the usual multistep syntheses. In preparative chemistry the MCRs of type III correspond to irreversible sequences of multistep procedures of forming the products. In living cells any formation of products from more than two biochemical materials corresponds to MCRs of type III. In our world the libraries of organo-chemical compounds began to exist 4.6 billion years ago. Then also the libraries of type I and II of MCRs were formed. Later developments brought about the formation of living cells, whose necessary biochemical compounds began to exist. Most of such biochemical compounds are specifically produced at the desired specific microplaces by sequences of enzymatically catalyzed specific biochemical reactions towards their preferred direction. Practically all such compounds are microparts of their living cells, whose formations from many educts correspond to MCRs of type III. Here the historical development of naturally occurring as well as of the preparative MCRs is described, and the modern formation, procedures, investigations, and systematic planning methods of the MCRs and their libraries are discussed. The α-aminoalkylation of nucleophiles introduced in 1850 is MCRs of type I. A little later the chemistry of the isocyanides began. However, for a whole century this chemistry remained a rather empty part of organic chemistry. An exception was the reaction of Passerini, the P-3CR of type IIB, introduced and investigated in 1921–31. Since 1958 isocyanides are well available, and a little later their Four Component Reaction

(U-4CR) and related reactions of five components were introduced; a few years later also their libraries of the simultaneously formed collections of products were introduced. In 1993 it was realized that unions of the U-4CR and several other reactions and MCRs had been introduced; thus MCRs of seven and later even more components were introduced. A few years later the chemistry of such MCRs and their libraries became in the chemical industry one of the most efficient, intense and successful methods of searching for new desirable chemical products. In the USA this methodology is most actively applied, and besides the four decades old term 'Ugi Reaction' now also the term 'Ugi Chemistry' is mentioned. The latter refers to a whole collection of chemical, mathematical, and computer oriented methods that were introduced between 1958 and now by Ugi and his co-workers.

Key words: MCR types I, II, and III; isocyanides; heterocycles; libraries.

INTRODUCTION

In principle, all chemical reactions are equilibrating interconversions of one or two educts and products. However, the preferred preparative reactions are practically irreversible procedures. If a chemical product is formed from three or more educts, usually a sequence of several chemical procedures is carried out. Nowadays more and more collections of many educts are directly converted into their products by one-pot multicomponent reactions (MCRs) since these have great preparative advantages.

The conventional multistep syntheses need increasing amounts of work, and their yields decrease with each step not only by many chemical reactions but also by isolations and purification of products. On the other hand, the MCRs with irreversible final steps need almost no preparative work, and large yields of pure products result, if no by-products are formed by competitive reactions.

The MCRs do not convert their collections of components simultaneously in single steps, but undergo many sub-reactions of one or two components, so that the final steps of these sequences lead to the products and by-products. These steps of MCRs can equilibrate, or they can be practically irreversible, determining the yields and purities of the products of the MCRs.

THE EARLY MCR CHEMISTRY OF OUR WORLD, INCLUDING THE LIVING CELLS

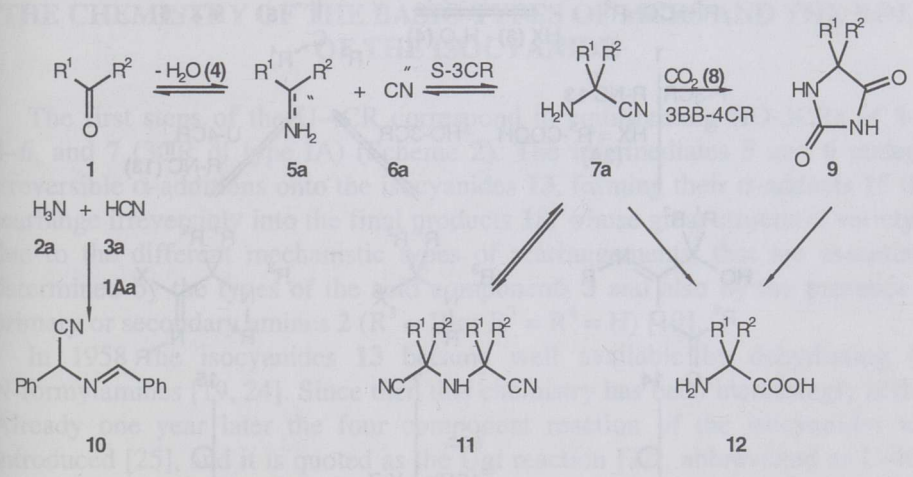
The libraries of organo-chemical compounds have existed for 4.6 billion years. In the natural atmosphere these chemicals were then formed, and still now not only conventional chemical reactions of two components take place but also a variety of MCRs participate. Not only single products but collections of many different chemicals were formed. These are nowadays referred to as libraries. In the nature, the usual chemical reactions and the MCRs and their libraries participated. This was demonstrated by Miller's famous experiment that produces educts of an MCR, forming natural building blocks [1–7] of the

aminoacids via the S-3CR [8]. As sufficient concentrations of these educts were probably too low for most such reactions, their formations could have taken place on mineral surfaces [6, 7].

A little later the living cells began to exist. These contain libraries of many different chemical products of MCRs. All of their temporary educts and products are formed by enzymatically accelerated reactions, so that these are preferred over their by-products. The living cells generate continuously great collections of chemical compounds as libraries. Most of their enzymatically formed products are 'purified' by enzymatic removal of the simultaneously formed impurities [9].

THE START AND GROWTH OF THE PREPARATIVE CHEMISTRY OF MCRs

The first man-made MCR was introduced in 1838 by Laurent & Gerhardt [10] who converted oil of bitter almonds and ammonia into a crystalline product **10** of an MCR of the twice reacting benzaldehyde **1Aa** ($R^1 = H$, $R^2 = Ph$), ammonia **2a**, and hydrogen cyanide **3a** (Scheme 1) [11].



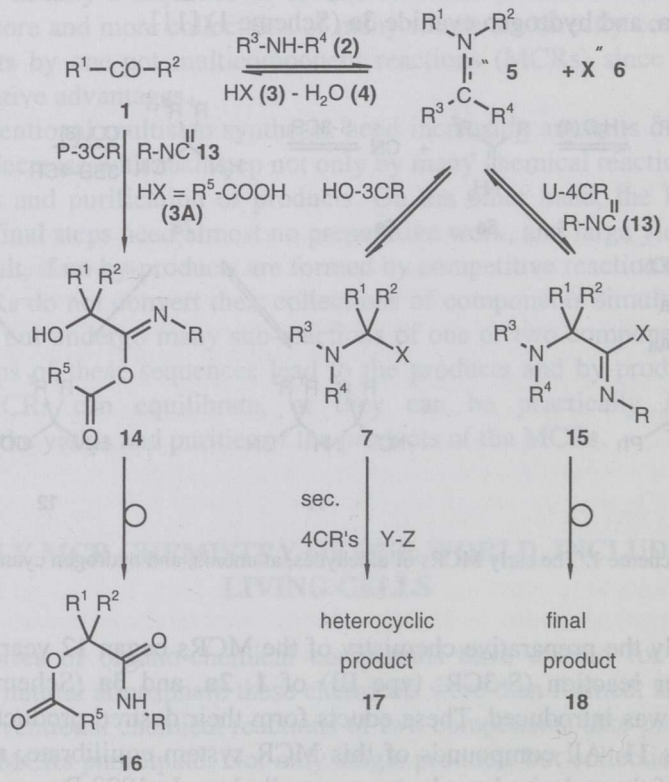
Scheme 1. The early MCRs of aldehydes, ammonia, and hydrogen cyanide.

Officially the preparative chemistry of the MCRs began 12 years later, when the Strecker reaction (S-3CR; type IB) of **1**, **2a**, and **3a** (Schemes 1 and 2) [8, 12–15] was introduced. These educts form their desired products **7a** and the by-products **11**. All compounds of this MCR system equilibrate, and therefore the yields of these desired products are usually low. In 1929 Bergs and Bucherer introduced their reaction (BB-4CR) [11, 16–19], by combining the educts **1**, **2a**, and **3a** of the S-3CR with CO_2 **8**, forming the hydantoin derivatives **9** in very high yields. This is due to the irreversible final formation of **9**, whose hydrolysis

is nowadays the preferred method of preparing the α-aminoacids **12** (Scheme 1). Since these are much better obtained via the BB-4CR than by the S-3CR, this old reaction is not used much any more.

The last irreversible step of converting the compound **7a** of the reversible S-3CR (MCR of type IB) into its BB-4CR product **9** (MCR of type IIB) illustrates particularly well the difference between these two different types of MCRs.

The era of finding old or new α-aminoalkylating 3CRs ended [12–15] when Hellmann and Opitz had published their book α-*Aminoalkylierung* in 1960 [11]. They had realized that most of the then known MCRs are 3CRs by α-aminoalkylations of nucleophiles, forming α-aminoalkyl compounds (**1–3** → **7**; Scheme 2). In some cases they proceed further with bi-functional reagents, yielding heterocycles [11]. These reactions belong to a collection of related 'name reactions' and similar MCRs. This collection of 3CRs of type IB is now also referred to as the Hellmann–Opitz reaction, the HO-3CR.



Scheme 2. Three basic types of MCRs that have in common carbonyl compounds **1** and deprotonable acid component **3**, together with one or two other educts. Their educts must be able to equilibrate with cations and anions, which react further towards their products **16**, **17**, or **18**.

THE EARLY CHEMISTRY OF THE ISOCYANIDES

The first isocyanide **13** was prepared in 1859 [19], but for a whole century the isocyanides were not well available, since no good method of their preparation existed yet. Therefore, and due to the intense foul smell of the isocyanides, their chemistry remained a rather neglected part of organic chemistry. One of the few exceptions was the intensively investigated Passerini reaction [P-3CR], in the period of 1921 till 1932 (Scheme 2; **1** + **3A** + **13** → **16**) [19–23], which was the first MCR of the isocyanides (MCR of type IIA); this chemistry was extended later.

The isocyanides are the only stable organic chemical compounds whose functional groups contain a divalent carbon atom C^{II}, and all of their chemical reactions correspond to exothermic irreversible transitions of C^{II} into C^{IV}. The preparative advantages of the isocyanide chemistry were realized, particularly in connection with their MCRs and libraries. The chemistry of the isocyanides became generally important since the 1990s. This is now a widely applied methodology, especially in the chemical industry [12–15].

THE CHEMISTRY OF THE BASIC TYPES OF MCRS AND THE ROLE OF THE ISOCYANIDE

The first steps of the U-4CR correspond to equilibrating HO-3CRs of **1–3**, **4–6**, and **7** (3CR of type IA) (Scheme 2). The intermediates **5** and **6** undergo irreversible α-additions onto the isocyanides **13**, forming their α-adducts **15** that rearrange irreversibly into the final products **18**, whose great structural variety is due to the different mechanistic types of rearrangements, that are essentially determined by the types of the acid components **3** and also by the presence of primary or secondary amines **2** (R^3 = H or $R^3 = R^4$ = H) [19].

In 1958 the isocyanides **13** became well available by dehydrating the N-formylamines [19, 24]. Since then this chemistry has been increasingly active. Already one year later the four component reaction of the isocyanides was introduced [25], and it is quoted as the Ugi reaction [22], abbreviated as U-4CR [14, 15]. The U-4CR and its unions with further reactions are nowadays one of the most active parts of organic chemistry [12, 13].

It was realized that the U-4CRs of chiral primary amine components proceed stereoselectively [19], and the courses of these reactions depend very much on the reaction conditions. Even the concentrations of their educts have often a strong interference on the course of U-4CRs [19, 26–28]. Therefore it was assumed that different reaction conditions of the U-4CRs can lead to quite different types of its reaction mechanisms. A model reaction of the U-4CR of a chiral amine was investigated.

In sharp contrast to the P-3CR [29], chiral isocyanides do not induce stereoselective U-4CR.

The U-4CRs proceed much faster and usually in better yields if the compounds **1** and **2** are pre-condensed into their Schiff bases, enamines, or aminals [19, 26–28]. As a stereoselective model reaction the isobutyraldehyde-(S)-α-phenylethylene imine **A** was reacted with benzoic acid **B**, the **3Aa** (R^5 = Ph) and *t*-butyl isocyanide **13a** (R = tBu) in methanol at 0°C [10–19, 30, 31].

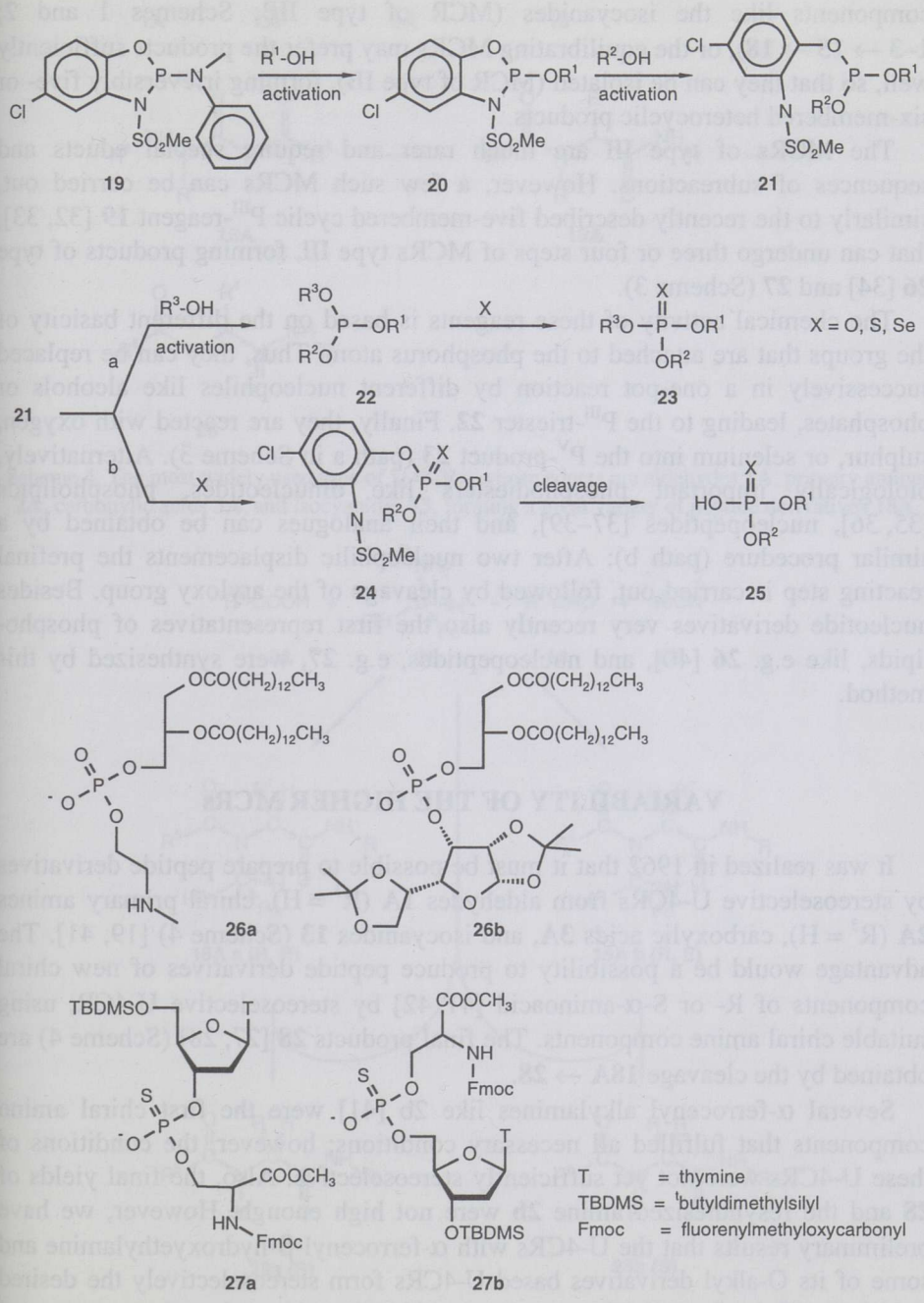
Two series of experiments were accomplished: In the first series, the equilibria of the starting materials **A** and **B** and the participating intermediates X_1–X_5 [30] were determined by measuring their electrical conductivities at various concentrations of **15** and **3Aa**. In the other series of experiments carried out, many different concentrations were formed into their diastereomeric products Y [19], whose ratios were then determined.

The resulting experimental data were evaluated by solving a rather complicated mathematical problem applying a computer-assisted method. Thus the reaction mechanism could be determined, which was one of the first solutions of a scientific problem where a combination of chemistry, physical data, mathematics, and computer methodology was used. Then it was also quite generally realized that such unions of different fields can be very successful, leading to a new type of chemical logic of reasoning, understanding, and planning in chemistry, including one of the first such computer programs [31].

The knowledge acquired from the book α-*Aminoalkylierung* [11] and the investigation of the stereoselective reaction mechanism of the U-4CR made it clear which basic reversible and partly irreversible types of MCRs play an important role. Then the question about the existence of MCRs that are sequences of irreversible subreactions arose. The answers to this question became a new grammar and classification of MCRs [12, 13]:

- Type IA: All starting materials, intermediate products, and final products participate with mobile equilibria, so that their products are usually not isolatable.
- Type IB: All starting materials, intermediates, and products participate with mobile equilibria, but the products are so stable that they can be isolated.
- Type IIA: The intermediate products of type IIA and IB react with a further educt, forming the final products irreversibly, and the number of formed chemical bonds increases.
- Type IIB: The pre-final products of type IA or IB react irreversibly with further multifunctional components and form heterocyclic products irreversibly, and the formed number of chemical bonds stays constant.
- Type III: The educts of MCR form one-pot products by sequences of irreversible subreactions.

Both the BB-4CR and the U-4CR start with essential equilibria of the three first components and form irreversibly the final products. However, they differ in some essential aspects. Most of the known MCRs belong to equilibria, and their products are so stable that they can be isolated (MCR of type IA), although they react further irreversibly. Other MCRs have intermediate products that are



Scheme 3. An MCR of type III, where a cyclic P^{III}-derivative **19** reacts stepwise.

so unstable that they cannot be isolated and undergo reactions with further components like the isocyanides (MCR of type IIB; Schemes 1 and 2; **1–3** → **15** → **18**), or the equilibrating MCRs may prefer the products sufficiently well, so that they can be isolated (MCR of type IB), forming irreversibly five- or six-membered heterocyclic products.

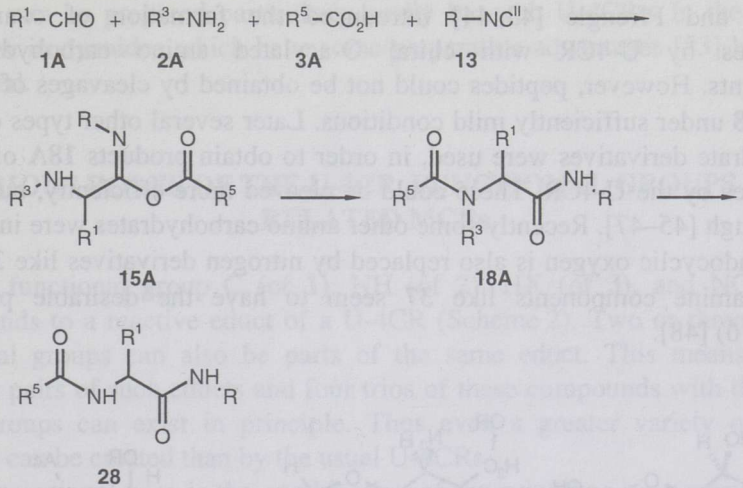
The MCRs of type III are much rarer and require special educts and sequences of subreactions. However, a few such MCRs can be carried out, similarly to the recently described five-membered cyclic P^{III}-reagent **19** [32, 33], that can undergo three or four steps of MCRs type III, forming products of type **26** [34] and **27** (Scheme 3).

The chemical activity of these reagents is based on the different basicity of the groups that are attached to the phosphorus atom. Thus, they can be replaced successively in a one-pot reaction by different nucleophiles like alcohols or phosphates, leading to the P^{III}-triester **22**. Finally, they are reacted with oxygen, sulphur, or selenium into the P^{V}-product **23** (path a in Scheme 3). Alternatively, biologically important phosphodiesters like dinucleotides, phospholipids [35, 36], nucleopeptides [37–39], and their analogues can be obtained by a similar procedure (path b): After two nucleophilic displacements the prefinal reacting step is carried out, followed by cleavage of the aryloxy group. Besides nucleotide derivatives very recently also the first representatives of phospholipids, like e.g. **26** [40], and nucleopeptides, e.g. **27**, were synthesized by this method.

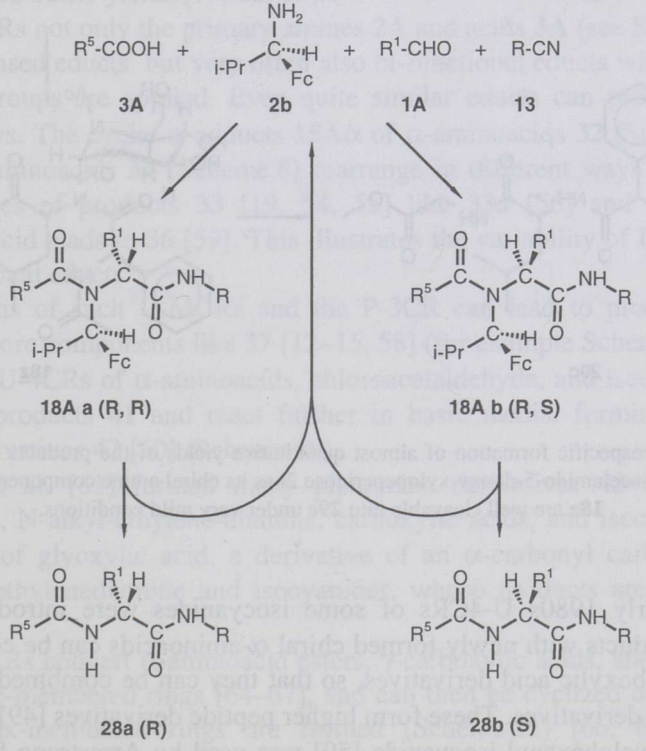
VARIABILITY OF THE HIGHER MCRs

It was realized in 1962 that it must be possible to prepare peptide derivatives by stereoselective U-4CRs from aldehydes **1A** (R^1 = H), chiral primary amines **2A** (R^3 = H), carboxylic acids **3A**, and isocyanides **13** (Scheme 4) [19, 41]. The advantage would be a possibility to produce peptide derivatives of new chiral components of R- or S-α-aminoacid [41, 42] by stereoselective U-4CR, using suitable chiral amine components. The final products **28** [27, 28] (Scheme 4) are obtained by the cleavage **18A** → **28**.

Several α-ferrocenyl alkylamines like 2b [41] were the first chiral amino components that fulfilled all necessary conditions; however, the conditions of these U-4CRs were not yet sufficiently stereoselective. Also, the final yields of **28** and the resynthesized amine **2b** were not high enough. However, we have preliminary results that the U-4CRs with α-ferrocenyl-β-hydroxyethylamine and some of its O-alkyl derivatives based U-4CRs form stereoselectively the desired products sufficiently well. Their products will be cleavable and can be re-converted into amine (Scheme 5).

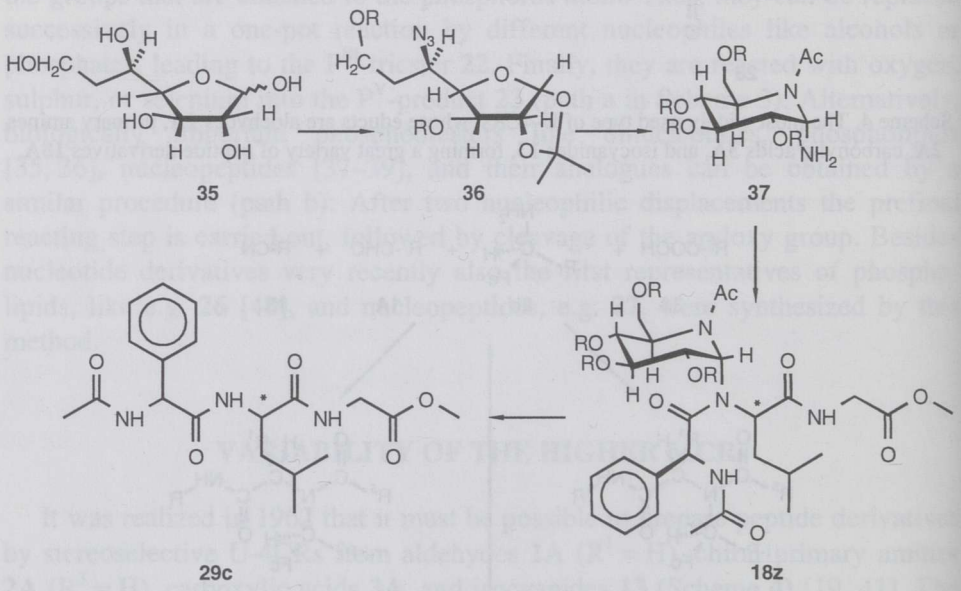


Scheme 4. The most widely used type of U-4CRs, whose educts are aldehydes **1A**, primary amines **2A**, carbonylic acids **3A**, and isocyanides **13**, forming a great variety of peptide derivatives **18A**.



Scheme 5. Stereoselective formation of α-aminoacid derivatives **18A a** or **b**, which can be protonated so that **28a** or **b** are formed, and the conversion of **18A** into **28** takes place so that simultaneously also the initial chiral amine **2b** can be resynthesized. In principle this is an almost optimal scheme of synthesis by a U-4CR; however, in practice such procedures do not form sufficient yields and purities of products.

Kunz and Pfrengle [43, 44] introduced the formation of α-aminoacid derivatives by U-4CR with chiral O-acylated amino carbohydrates as components. However, peptides could not be obtained by cleavages of the type **18a** → **28** under sufficiently mild conditions. Later several other types of amino carbohydrate derivatives were used, in order to obtain products **18A** of peptide derivatives by the U-4CR. These could be cleaved more efficiently, but not yet well enough [45–47]. Recently some other amino carbohydrates were introduced whose endocyclic oxygen is also replaced by nitrogen derivatives like **35** → **37**. Such α-amine components like **37** seem to have the desirable properties (Scheme 6) [48].



Scheme 6. Stereospecific formation of almost quantitative yields of the products **18z** by U-4CRs with 1-amino-5-acetamido-5-deoxy-xylopeperidose 2i as its chiral amine component. The products **18z** are well cleavable into **29c** under very mild conditions.

In the early 1980s U-4CRs of some isocyanides were introduced, whose resulting products with newly formed chiral α-aminoacids can be converted into activated carboxylic acid derivatives, so that they can be combined with further α-aminoacid derivatives. These form higher peptide derivatives [49].

The Δ^1–cyclohexenyl-isocyanide [50] was used by Armstrong [51, 52], who introduced the removal of the N–Δ^1–cyclohexenyl group from the U-4CR products so that these can then react further, forming a great variety of chemical compounds. In the 1970s Joullié [42] had found that many types of natural

products can be prepared particularly easily by such U-4CRs. In the last few years new isocyanides which have some preparative advantages [53] have been introduced.

VARIOUS ROLES OF THE U-4CR, FUNCTIONAL GROUPS AND RELATED MCRs

Each functional group C (of **1**), NH (of **2**), HX (of **3**), and NC (of **13**) corresponds to a reactive educt of a U-4CR (Scheme 2). Two or three of these functional groups can also be parts of the same educt. This means that six different pairs of such educts and four trios of these compounds with three such active groups can exist in principle. Thus even a greater variety of U-4CR products can be created than by the usual U-4CRs.

An exceptional case is the combination of the primary amino group and the carbonyl group, when these components are precondensed into their Schiff bases. They have the same products as those of **1** and **2A**, but are usually formed faster and have better yields [19, 22, 23].

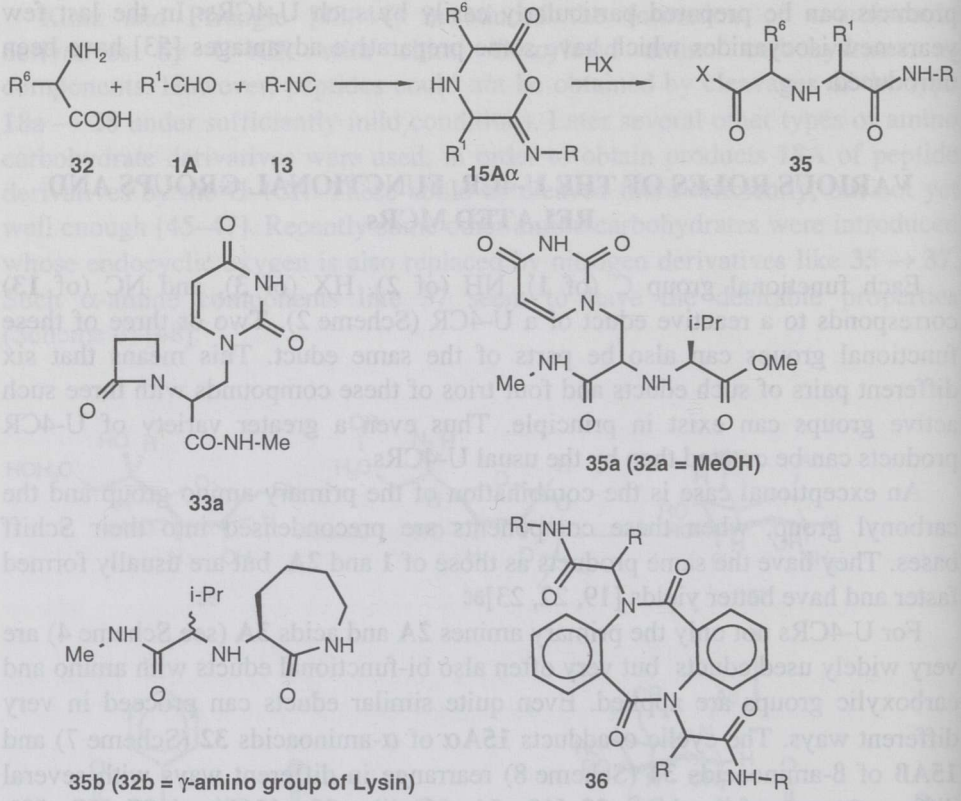
For U-4CRs not only the primary amines **2A** and acids **3A** (see Scheme 4) are very widely used educts but very often also bi-functional educts with amino and carboxylic groups are applied. Even quite similar educts can proceed in very different ways. The cyclic α-adducts **15Aα** of α-aminoacids **32** (Scheme 7) and **15Aß** of ß-aminoacids **34** (Scheme 8) rearrange in different ways with several different types of products **33** [19, 54, 55] like **33a** [56] and **35** [57, 58]. Anthranilic acid leads to **36** [59]. This illustrates the variability of U-4CR by bi- and trifunctional educts.

The unions of such U-MCRs and the P-3CR can lead to products of six, seven, and more components like **37** [12–15, 58] (for example Scheme 9).

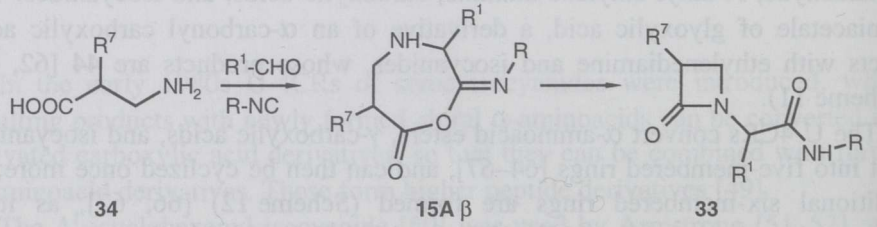
Thus the U-4CRs of α-aminoacids, chloroacetaldehyde, and isocyanides lead first to the products **41** and react further in basic media, forming ultimately aziridine derivatives **42** [60] (Scheme 10).

Rossen et al. [61] formed many piperazine derivatives **43** from chloro-acetaldehyde, N-alkyl-ethylene-diamine, carboxylic acids, and isocyanides. The hemiacetale of glyoxylic acid, a derivative of an α-carbonyl carboxylic acid, reacts with ethylenediamine and isocyanides, whose products are **44** [62, 63] (Scheme 11).

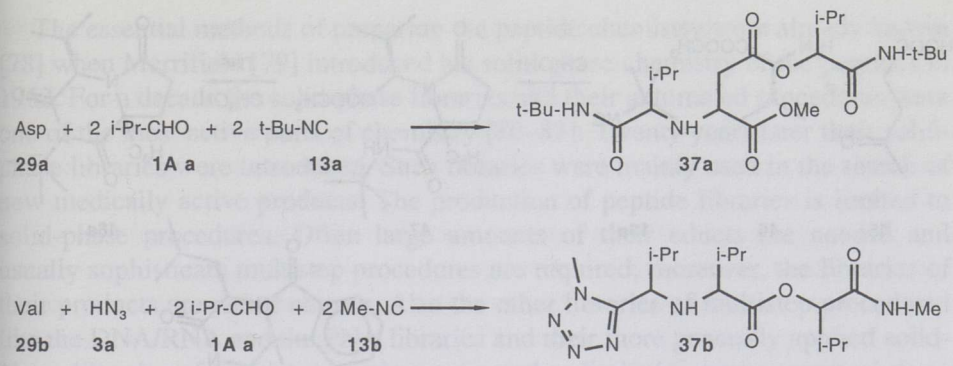
The U-4CRs convert α-aminoacid esters, γ-carboxylic acids, and isocyanides first into five-membered rings [64–67], and can then be cyclized once more; so additional six-membered rings are formed (Scheme 12) [66, 67], as it is illustrated by the reaction of **13a**, **45**, and **46** via **47** to **48a**, and the conversion of 2-carboxybenzaldehyde into the tri-cyclic compound **48b**.



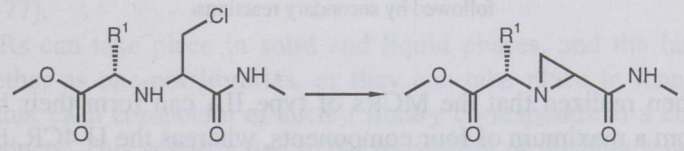
Scheme 7. Formation of cyclic α-adducts **15Aα** from α-aminoacids by U-4CRs, that react further with nucleophiles, and lead to products of type **35**, whereas the 'U-4CR' of anthranilic acid forms products of type **36**.



Scheme 8. Conversion of ß-aminoacids **34** into ß-lactam derivatives like **33a** (see Scheme 7).

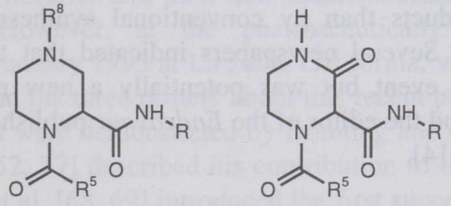


Scheme 9. Formation of the products **37a** and **b** by MCRs with seven reactive groups participating. Two of the educts are equal. Such MCRs are unions of P-3CRs and U-4CRs.



41 **42**

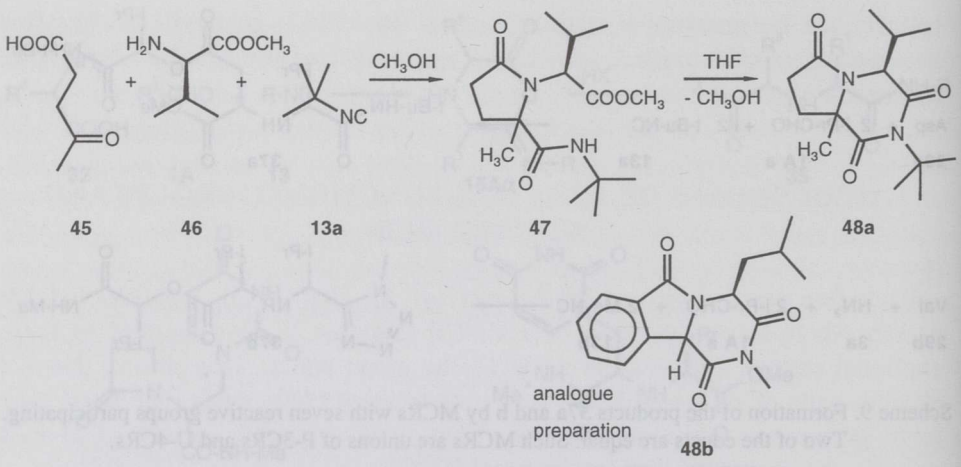
Scheme 10. Formation of aziridine derivatives **42** by U-4CRs of chloroacetaldehyde, followed by alkaline cycloalkylations.



43 **44**

Scheme 11. Formation of piperazine derivatives by U-4CR and their secondary reactions of ethylene diamine (like **44**) or their N-alkyl derivatives (like **43**).

After more than a century the HO-3CRs and the chemistry of the isocyanides came together, and led to a new era of the U-4CR chemistry. However, for more than three decades this chemistry was not of much general interest, but since 1993, quite suddenly the chemistry of the isocyanides became intellectually and practically extremely attractive, particularly in the chemical industry [68–70].



Scheme 12. MCRs of α-aminoacids, like **46**, the γ-carbonylcarboxylic acid **45**, and isocyanides **13a** followed by secondary reactions.

It was then realized that the MCRs of type IIA can form their heterocyclic products from a maximum of four components, whereas the U-4CR, the union of the P-3CRs and HO-3CR as the HO-3CR ∪ P-3CR, can form further unions with other chemical reactions of MCRs [14, 15]. The representation of 7CRs is demonstrated. According to various journals [71–74], in such new types of MCRs, in principle, unlimited numbers of components can participate [12, 13]. The publication about the first one-pot MCRs of seven different components demonstrated that their products are thus formed much easier and usually in better yields of products than by conventional syntheses [71] of the usual multistep sequences. Several newspapers indicated that this was not only an unusual entertaining event but was potentially a new profound progress in chemistry [72, 73], and the editor of the *Endeavour* published a review about the new types of MCRs [14].

THE CHEMISTRY OF LIBRARIES

As soon as the organic chemistry had started in this world, also MCRs and the formation of their libraries began. Less than a billion years later the life of few living cells and their biochemistry of the MCRs and their libraries appeared.

The preparative chemistry of the MCRs was introduced around the middle of the last century. However, their libraries were proposed more than a century later [19, 70, 75].

The solid phase peptide libraries were introduced in 1982 by Furka [70, 76]. Soon many other authors entered this field [77] of experimental production and investigation.

The essential methods of preparing the peptide chemistry were already known [78] when Merrifield [79] introduced his solid-phase chemistry of the peptides in 1962. For a decade the solid-phase libraries and their automated procedures were one of the most active parts of chemistry [80–83]. Twenty years later their solid-phase libraries were introduced. Such libraries were mainly used in the search of new medically active products. The production of peptide libraries is limited to solid-phase procedures. Often large amounts of their educts are needed and usually sophisticate multistep procedures are required; moreover, the libraries of their products are rather narrow. Also the other libraries of multistep procedures like the DNA/RNA and the PNA libraries and their more generally applied solid-phase libraries of multistep syntheses are rather limited, whereas most of these disadvantages can be avoided when MCR libraries are produced. However, it was gradually realized that such libraries were not sufficiently variable [70]. In the late 1980s also solid-phase libraries of various multistep syntheses were introduced, but a sufficient variety of chemical reactions could not thus be carried out [77].

The MCRs can take place in solid and liquid phases, and the latter can be formed together as one-pot libraries, or they can take place in many different vessels, so that each compound of such a library corresponds to a collection of separate products. This is partly due to the possibility of forming relatively high yields of rather pure products. Many such MCRs proceed very quickly and can be automated much easier than the multistep libraries.

For a very long time the MCRs of the isocyanides and their libraries were of little general interest. Still at the GDCh-workshop conference of 16–18 November 1994 at Bitterfeld, Germany, practically no attention was paid to the progress of the MCR libraries and their new mathematically oriented computer methodology [84]. However, at the pharmaceutically oriented chemical conference of 23–25 January 1995 at La Jolla, California, very many colleagues showed great interest in the three posters about this recent progress of the MCRs and their libraries that were demonstrated by Dömling and Gruber [85]. Shortly later Armstrong [51, 52, 77] described his contribution to the solid-phase MCR libraries, and Weber et al. [68, 69] introduced the first successful union of many different types of industrial research of sophisticated planning and their preparative, analytical, and computer-assisted, maximally automated chemical methods, which proceed much more efficiently than the other activities [68, 70, 77].

PERSPECTIVES

In recent years, the chemistry of the isocyanide MCRs and their libraries has become one of the most active fields of industrial organo-chemical research and connected methods of investigation, particularly in the USA, Switzerland, and

Japan, since this one-pot chemistry can be carried out much more conveniently, efficiently, and variably than any previously used collections of methods. This recent progress is partly due to the fact that most of the essential methods and ideas concerning the MCR chemistry of the isocyanides had been introduced in the last four decades, and some of this progress had already been made in the last century.

Lately the combinatorial chemistry of the MCRs and a great variety of connected sciences have been one of the most widely and often used area of the industrial chemical research. The planning, investigation, and production of improved or completely new desirable products proceed nowadays by many orders of magnitude, quicker, and more efficiently than any previous collection of methods. This is certainly one of the essential areas of theoretical and applied parts of progress in the last four years, and they will continue in the next century.

This almost sudden progress is mainly due to the fact that many ideas that were long known, concepts, methods, and techniques of various fields of science and technology were and are still combined, and these are now very widely applied by the chemical industry. This fast progress exists partly because many research groups had realized almost suddenly that this methodology can have many advantages over all previous methods. The new chemistry can be accomplished almost directly by well known methods of long ago. However, much further progress can still be made.

For a few years very many MCRs can lead to almost quantitative yields of products, and if chiral educts are used, even highly stereoselective MCRs can be carried out. However, such favourable procedures can only take place if the optimal components and reaction conditions are used.

The living cells accomplished the chemistry of the MCR libraries by enzyme-assisted procedures more than four billion years ago. The preparative MCR library chemistry and automated procedures with mathematically oriented computer methods are presently very active and have been so for a few years. One further essential step of profound progress has not yet been accomplished efficiently, namely suitable and efficient catalysts and enzymes, together with their suitable methodology, have not yet been found.

Although industry wants and needs quick progress, universities and independent research institutes are not yet active in this field. They could be very productive in the optimal exploration and application of the MCR libraries. These require a variety of mathematically oriented computer-assisted procedures [68, 69, 84, 86]. In order to receive extremely high yields and purities, the MCRs need always the optimal reacting conditions, and this is not yet easy. The best reaction conditions of forming the optima of MCR product libraries are even much more difficult to be found than optimizing the formation of single MCR products. It is important to develop further automatic equipment and mechanical, mathematical, and computer-oriented development methods.

It is quite sure that the chemistry of the MCRs and their libraries will not be given due to being replaced by some other methodology. On the contrary, it will

be improved continuously and this field of science will also be pursued in the next century.

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MKR XXIII. UGI MULTIKOMPONENTSED REAKTSIOONID EILE, TÄNA JA HOMME, NENDE PREPARATIIVSE JA TEOREETILISE KEEMIA MITMEKÜLGSED MULTIDISTSIPLINAARSED VÕIMALUSED

Ivar Karl UGI

Orgaanilises keemias on kolm multikomponentsete reaktsioonide (MKR) põhitüüpi. MKR-d ei leia aset otseselt, vaid kujutavad endast kahekomponentsete reaktsioonide süsteeme. I tüüpi MKR-de puhul on kõik allreaktsioonid tasakaalulised. II tüübi puhul enamik allreaktsioone küll tasakaalustub, kuid lõpp-produkti moodustumine on pöördumatu. II tüüpi MKR-d kulgevad alates kahest esimesest lähteainest lõpp-produktini pöördumatute reaktsioonide kujul. Sellised reaktsioonid on preparatiivses keemias suhteliselt haruldased, kuid neil on täita küllaltki oluline osa elusorganismides.

MKR-de produktipangad kujunesid koos orgaaniliste ühendite tekkega meie maailma ligikaudu 4,5 miljardit aastat tagasi. Hilisem areng viis välja elusrakkude tekkeni. Neist enamiku osalus biokeemilistes reaktsioonides tuleneb lokaliseeritud MKR-des ensümaatiliselt katalüüsitud spetsiifiliselt kiirendatud reaktsioonidest. 1850. aastal esitatud nukleofiilide α-aminoalkülatsioonidest kuulusid esimesed just I tüüpi MKR-de hulka. Veidi hiljem sai alguse isotsüaniidide keemia, kuid isotsüaniidide saamise keerukuse tõttu ei pööratud sellele valdkonnale terve sajandi vältel tähelepanu. Erandiks oli siiski Passerini kolmekomponentne reaktsioon (II tüüp – P-3CR). Alates 1958. aastast muutus isotsüaniidide saamine lihtsaks, kui lisandusid Ugi neljakomponentne reaktsioon (U-4CR) ja selle produktipangad. Umbes samal ajal teostati ka esimesed viiekomponentsed reaktsioonid, kuid alles alates 1993. aastast on kasutusel isotsüaniidide seitsme või enama komponendiga MKR-d. Selliste kõrgemate MKR-de tulemusel moodustuvad kahe või kolme MKR-i ühendused. Nüüdseks on isotsüaniidide keemia aktiviseerunud ja muutunud keemiatööstuses kõige intensiivsemalt rakendatavaks keemia haruks, sest see võimaldab saada soovitud ühendeid kiiremini ja efektiivsemalt kui kunagi varem.