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FAST AND PERMANENT CHANGES IN PREPARATIVE AND PHARMACEUTICAL CHEMISTRY THROUGH MULTICOMPONENT REACTIONS AND THEIR 'LIBRARIES'

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Dedicated in the 65th year of Ivar Ugi [79b] to the 85th, 80th, 75th, 70th, 65th, and 60th birthdays of his admired colleagues, professors
Wang Yu [66a],
Miklos Bodanszky [56, 62b],
Sir Derek H. R. Barton [78], Jaques Emile Dubois, Rolf Huisgen [63], Jan Michalski,
Hans Jürgen Bestmann [66b], Albert Eschenmoser, Joshua Lederberg [82, 99], Paul A. D. de Maine, Max Schmidt,
Frank Albert Cotton, Heinz P. Fritz, Endel Lippmaa, Richard Neidlein [67], Milan Randiç, Colin B. Reese, Hans-Dieter Scharf, Paul von Ragué Schleyer [79], Mihkel Veiderma,
Reinhard Schmutzer, Hubert Schmidbaur, Kjell Sjöberg [5c, 51b], Nikolai S. Zefirov,
and also in fond memory of the ingenious mathematician James Dugundji [85], who passed away 10 years ago in 1985, and the life of Hans Fischer [90] and his important role in chemistry, that ended 50 years ago.

Abstract. Classical chemical syntheses from n materials are sequences of $\geq(n-1)$ preparative steps. Such products can now be made more efficiently by one-pot U-4CRs. (This reaction was first carried out in 1959.) There amines, carbonyl compounds, and many different types of acids undergo α-additions onto isocyanides. The rearrangements that follow lead to a greater variety of products than all the classical MCRs (Multi Component Reactions) together. Since 1993 MCRs of ≥5 components have been developed. These are unions of the U-4(5)CR and other 3(4)CRs.

In 1961 the first library of U-4CRs was proposed in *Isonitrile Chemistry*, and in the last few years libraries of MCRs have become very popular. This has led to important progress in preparative chemistry and pharmaceutical research. The biologically active chemical compounds of liquid MCR-libraries can be determined particularly easily through the development of new algebraic computer-assisted procedures.

Key words: classical 3CRs, α–aminoalkylations of nucleophiles, new chemistry of isocyanides, one-pot syntheses, MCRs of ≥4 reacting components, libraries of MCRs, progress in pharmaceutical chemistry.

Abbreviations: MCR: **M**ulti**C**omponent **R**eaction; 3, 4... etc.: number of reacting components; capital letters: abbreviations of name reactions, for example the S-3CR = **S**trecker's **3** **C**omponent **R**eaction; Me = Methyl, Et = Ethyl, iPr = iso-Propyl; nB = normal Butyl; tBu = tert.Butyl; Am = Amyl; cHex = cyclo-Hexyl; Ph = Phenyl; Bz = Benzyl; Pnb = pNitrobenzyl; Phth = Phthalyl.

1. INTRODUCTION

The syntheses of desired chemical products usually require many preparative steps, including the separation and purification of the various intermediates. Generally the final yields of such procedures are rather low.

In contrast, living cells form the desired compounds from their starting materials by rapid 'one-pot' procedures, and no starting materials are lost by competing formation of undesired by-products. Of course, there are many good reasons why the usual preparative organic chemistry cannot proceed similarly, but sometimes there are some analogous special cases. It was realized early on that in living cells a variety of polycyclic natural products like alkaloids, terpenes, and steroids, are made from multifunctional starting materials and unsaturated compounds. Similar chemical compounds can be formed directly by combinations of the Mannich, Knoevenagel, and Diels-Alder Reactions. There has been important progress in the syntheses of five- and six-membered cyclic natural products and analogous compounds [1, 2]. Such ideal models act as a benchmark with which one-pot MCRs can be compared.

A chemical compound produced by a living organism, irrespective of the number of starting materials, corresponds to high yields of a one-pot MCR.

In standard chemical reactions two compounds (A) and (B) are converted to the product (AB). In a few exceptional cases just one single starting material is converted into a product. In principle all such reactions are equilibria, but many of them are effectively irreversible [3].

When products are obtained from many starting materials, a sequence of several discrete steps is carried out. In each step only one or two of the participating compounds react. The greater the number of steps, the lower the final product yields will be.

In 1954 Woodward and his research group published the famous synthesis of strychnine in 28 steps with an overall yield of 0.00006% [4, 5a]. In the following 40 years the synthesis of strychnine has been improved greatly. Today it can be carried out in a sequence of "only" 25 reactions with a final yield of 3% [6, 7].

A few years ago, Heathcock et al. [2] prepared an equally complex natural alkaloid, daphniphylline, from a dialdehyde with five double bonds and a few other components, with 65%, essentially by a MCR [5a].

Over a period of more than 150 years MCRs have led to fundamental progress in organic chemistry [5, 8, 9], and during the next century MCRs will be an important part of preparative methodology. MCRs of three or more different monofunctional reacting components can be carried out in one preparative step. One-pot MCRs can produce chemical compounds by simply mixing the starting materials, products which otherwise can only be prepared by multistep procedures, often involving difficult isolation methods and resulting in much lower overall yields.

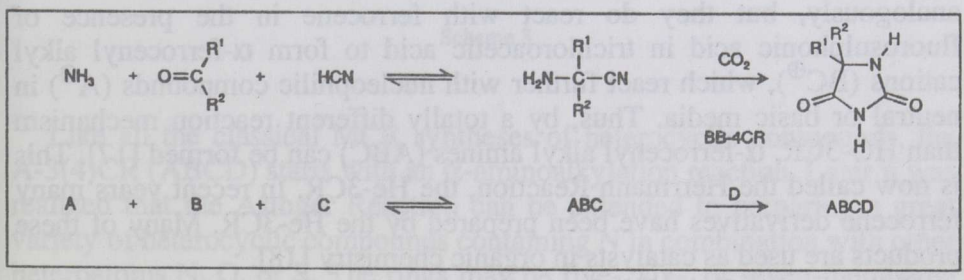
Ideal MCRs are also sequences of many reactions, in which one or two chemical compounds take part in each step; however, all these reactions equilibrate simultaneously, and only one or two final reactions are practically irreversible, resulting in the formation of the desired products. Any irreversible formation of by-products that may compete significantly should be avoided [10, 11d].

In principle both cases, the sequences of equilibria and the sequences of purely irreversible reactions, could form the products. No such perfect limiting cases of MCRs have yet been observed. Neither are all the steps completely reversible, nor are there complete sequences of irreversible reactions.

2. CLASSICAL MCRs

In 1850 Strecker [5, 9, 12] discovered that ammonia (A), carbonyl compounds (B), and hydrogen cyanide (C) react together into α-aminoalkylcyanide (ABC) *via* α-aminoalkylcations and the cyanide anion ($C^{\ominus}$).

This three component reaction, the Strecker Reaction (S-3CR), was the first classical MCR. It was quite popular, as its products could be converted into the desired α-aminoacids.



Scheme 1

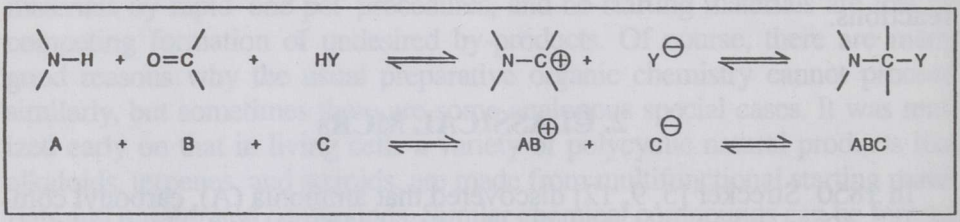
Yet in most equilibrating S-3CRs the yields were not satisfactory, and often toxic by-products were formed. In spite of this, preparations of various α-aminoalkylcyanides were popular, as the S-3CR is more efficient and less time consuming than any alternative synthesis of more steps.

The Mannich condensation was introduced in 1912 [5, 8, 13], and it is still one of the most widely used classical MCRs, although in the M-3CR the variations of starting materials and resulting products are rather limited, and the reactions do not always proceed well. Most M-3CRs are condensations between dialkylamines (A), formaldehyde (B), and carbonyl compounds (C), which form ß-dialkylamino carbonyl compounds (ABC). The M-3CRs correspond to equilibria between starting materials and products as well as α-dialkylaminomethyl cations ($AB^{\oplus}$) and anions of α-deprotonated carbonyl compounds ($C^{\ominus}$).

Already early some well-known natural products and analogous compounds were synthesized by Robinson [14] and later by Schöpf et al., who applied some interesting variations of the M-3CR [15].

Each one of these MCRs forms a certain type of product from a rather narrow collection of structurally analogous starting materials.

In their famous monograph α-*Aminoalkylierung* Hellmann and Opitz [9] realized that in addition to the classical MCRs many other similar 3CRs can take place (*Scheme 1*) where amines (A), carbonyl compounds (B), and weak acids HY (C) equilibrate not only with α-aminoalkyl cations ($AB^{\oplus}$), the anions ($C^{\ominus}$), and water, but also with the final products (ABC). This is referred to now as the Hellmann–Opitz Reaction, HO-3CR.



Scheme 2

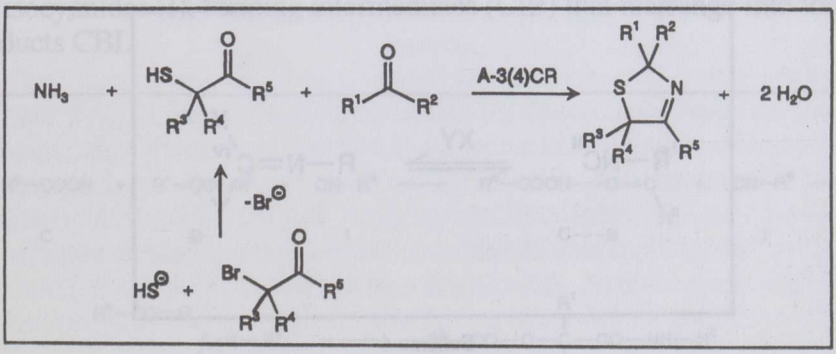
In weakly acidic media dimethylamine (A), formaldehyde (B), and ferrocene (C) first form ($AB^{\oplus}$), and this substitutes a proton of the ferrocene, forming the final product dimethylaminomethyl ferrocene (ABC) [16] as a HO-3CR. Other aldehydes and ketones (B) do not react analogously, but they do react with ferrocene in the presence of fluorosulphonic acid in trichloroacetic acid to form α-ferrocenyl alkyl cations ($BC^{\oplus}$), which react further with nucleophilic compounds ($A^{\ominus}$) in neutral or basic media. Thus, by a totally different reaction mechanism than HO-3CR, α-ferrocenyl alkyl amines (ABC) can be formed [17]. This is now called the Herrmann Reaction, the He-3CR. In recent years many ferrocene derivatives have been prepared by the He-3CR. Many of these products are used as catalysts in organic chemistry [18].

Hellmann and Opitz [9] also realized that many five- and six-membered heterocyclic compounds can be prepared by classical MCRs. Four component reactions begin with reversible 3CRs as α-aminoalkylations, forming intermediates ABC. These combine further with compounds (D). In the final steps such 4CRs and higher MCRs form heterocyclic products (ABCD) practically irreversibly.

With a few exceptions, all the classical MCRs are α-aminoalkylations of anions. Thus all of these name reactions and several other reactions of the same type are just one single general reaction, the equilibrating HO-3CR. These include α-aminoalkylations that are followed by secondary formations of heterocycles, by practically irreversible reactions with additional chemical compounds. Particularly famous are syntheses of five- and six-membered heterocyclic products of Hantsch [19] and Bignelli [20] by one-pot reactions of the last century.

In 1929 Bergs and Bucherer proposed the BB-4CR [11k, 21] (see *Scheme 1*), a typical example of obtaining a heterocyclic compound by a one-pot 4CR, beginning with an equilibration of the α-aminoalkyl cyanide (ABC) and by-products of the S-3CRs. This reacts further with CO_2 (D) and forms the heterocyclic hydantoin (ABCD). The yields of BB-4CRs are generally higher than in the comparable S-3CRs, due to the irreversible formation of these heterocyclic products. The BB-4CRs lead to products that are free from the reversibly formed toxic by-products. Therefore, the BB-4CR has replaced the old S-3CR completely in the preparation of α-aminoacids.

The preparation of 5,6-dihydro-2*H*-1,3-thiazine derivatives from three or four starting materials by the A-3(4)CR was discovered in 1958 by Asinger et al. [22].



Scheme 3

Like all the classical MCR syntheses of heterocyclic compounds, the A-3(4)CR (ABCD) starts with an α-aminoalkylation reaction. Later it was realized that the Asinger Reaction can be extended to preparing a great variety of heterocyclic compounds containing N in combination with other heteroatoms N, O, or S. The rings may be five-, six-, or seven-membered and contain a CN double bond. The A-3(4)CR can be considered as the last classical MCR of heterocyclic compounds [9, 23].

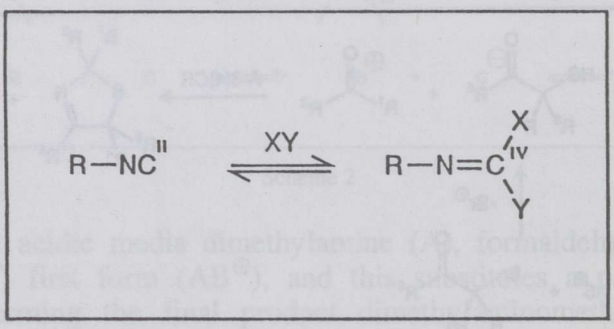
Preparation of chemical compounds by one-pot MCRs has the advantage that the syntheses require fewer chemical procedures. Furthermore, most MCRs have better yields. The classical MCRs have the disadvantage that their applications are generally limited to rather narrow

areas of chemistry. For instance, the products of the S-3CR or the BB-4CR correspond merely to variations of substituted carbonyl compounds.

3. CLASSICAL ISOCYANIDE CHEMISTRY

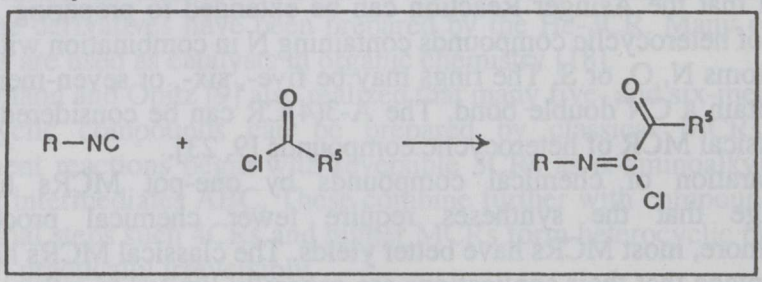
The first isocyanides were prepared by Lieke [24]. In 1859 he found that allyl iodide and silver cyanide form allyl isocyanide. In 1866 Meyer [25] produced methyl and ethyl isocyanide analogously, and a year later Gautier [26] generalized this method of preparing alkyl isocyanides. He had also tried to produce isocyanides from primary amine formiates by dehydrating these with P_2O_5, but he was unsuccessful, because the products were not protected from the acids [10b]. Shortly thereafter, in 1867, Hofmann [27] found a general method of isocyanide preparation from primary amines, chloroform, and potassium hydroxide.

The general reactivity of isocyanides was the subject of investigation for a relatively short period thereafter [11, 28]. It was realized that the chemistry of the isocyanides is completely different from the rest of organic chemistry. Isocyanides are the only stable organic chemical compounds which contain divalent carbon, C^{II}. This is always formed from a starting material with a functional group of C^{IV}, which can be converted into the isocyanide group with its C^{II}. The isocyanides are always made by $C^{IV} \rightarrow C^{II}$ processes [11a]. All known chemical reactions of isocyanides correspond to $C^{II} \rightarrow C^{IV}$.



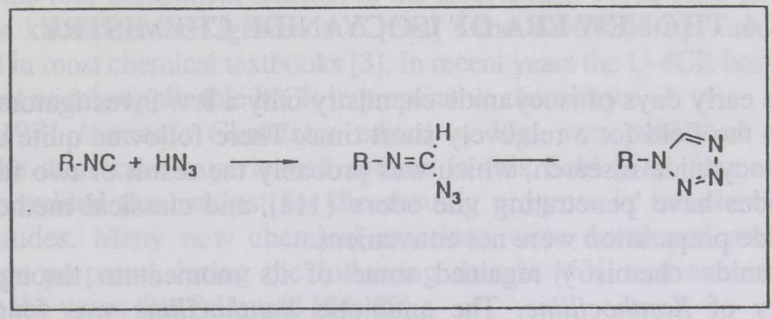
Scheme 4

Apart from the thermal rearrangement of isocyanides into cyanides, the classical chemical reactions of isocyanides are insertions into chemical compounds. Some products are formed directly by α-additions onto isocyanides. An example is their reaction with acid chlorides, which was discovered by Nef [28].



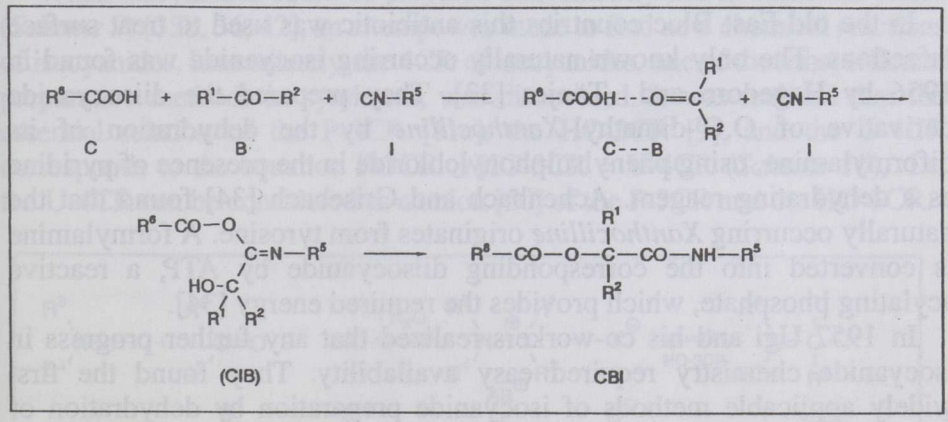
Scheme 5

Other compounds react to form intermediates by α-additions onto isocyanides, which then lead to the final products by rearrangements, e.g. the α-addition of hydrazoic acid onto isocyanides with a subsequent rearrangement into N-substituted tetrazoles by Oliveri–Mandala and Alagna [11, 29].



Scheme 6

The classical period of isocyanide chemistry ended with the discovery of Passerini's three component reaction, the P-3CR, in which α-acyloxy-carbonamides are formed from carbonyl compounds (B), carboxylic acids (C), and isocyanides (I). This reaction was investigated between 1921–31 [11c, 30, 31]. Formally protonated carbonyl compounds, α-hydroxyalkyl cations ($B^{\oplus}$), and carboxylic anions ($C^{\ominus}$) undergo α-additions onto the C^{II} atoms of the isocyanides (I), forming intermediates (CIB) that rearrange into the final products CBI.



Scheme 7

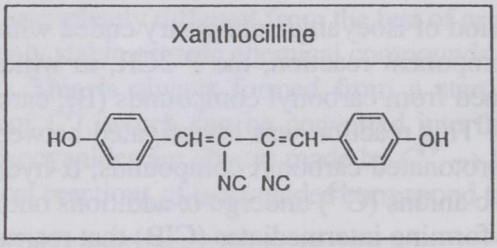
On the one hand, the P-3CR can obtain the α-hydroxyalkyl isocyanide cations ($IB^{\oplus}$) by α-adding the O-protonated carbonyl compounds ($HB^{\oplus}$) to the isocyanides (I), and the products CIB by joining the cations ($IB^{\oplus}$) and the anions ($C^{\ominus}$). Thus both the P-3CR and the HO-3CR are unions of three components, resulting from the formation of cations of two of the starting materials and subsequently joining them to the anions, which are deprotonating anions.

On the other hand, the P-3CR can also take place by inserting isocyanides (I) into the carbonyl compounds and carboxylic acids which are 'joint α-adducts' (B···H-C) of hydrogen bridges.

4. THE NEW ERA OF ISOCYANIDE CHEMISTRY

In the early days of isocyanide chemistry only a few investigators were active in the field for a relatively short time. There followed quite a long lull in isocyanide research, which was probably the result of two factors: isocyanides have 'penetrating vile odors' [11a], and classical methods of isocyanide preparation were not convenient.

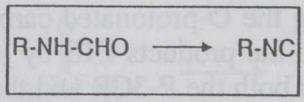
Isocyanide chemistry regained some of its momentum through the discovery of *Xanthocilline*. The antibiotic *Xanthocilline* was found by Rothe [32] in 1948, in cultures of *Penicillium notatum* and *P. chrysogenum*.



Scheme 8

In the old East Bloc countries this antibiotic was used to treat surface infections. The only known naturally occurring isocyanide was found in 1956 by Hagedorn and Tönjes [33]. They prepared the diisocyanide derivative of O,O'-dimethyl-*Xanthocilline* by the dehydration of its diformylamine, using phenylsulphonylchloride in the presence of pyridine as a dehydrating reagent. Achenbach and Grisebach [34] found that the naturally occurring *Xanthocilline* originates from tyrosine. A formylamine is converted into the corresponding diisocyanide by ATP, a reactive acylating phosphate, which provides the required energy [34].

In 1957 Ugi and his co-workers realized that any further progress in isocyanide chemistry required easy availability. They found the first widely applicable methods of isocyanide preparation by dehydration of N-formylamines with $POCl_3$ in the presence of various bases [11b, 35–37], remembering the role of P_2O_5 that Gautier had had in mind [26] and the ATP biochemistry of Achenbach and Grisebach [34].



Scheme 9

The widely applicable dehydrating reagents phosgene [11b, 37], diphosgene [38], or triphosgene [39] also have particular advantages. In a number of

special cases phenyl- and *p*-tolylsulphochloride form isocyanides well from derivatives of natural products [33, 40] and polymeric compounds [41].

As soon as isocyanides were easily available, new efforts began in developing *isocyanide chemistry* [11]. In 1959 Ugi and his co-workers [36, 42] introduced the four component reaction of the isocyanides. From 1962 onwards it became known as the Ugi Reaction [31a] – the U-4CR [11d] – and is now quoted in most chemical textbooks [3]. In recent years the U-4CR has become the most widely applicable MCR in preparative chemistry.

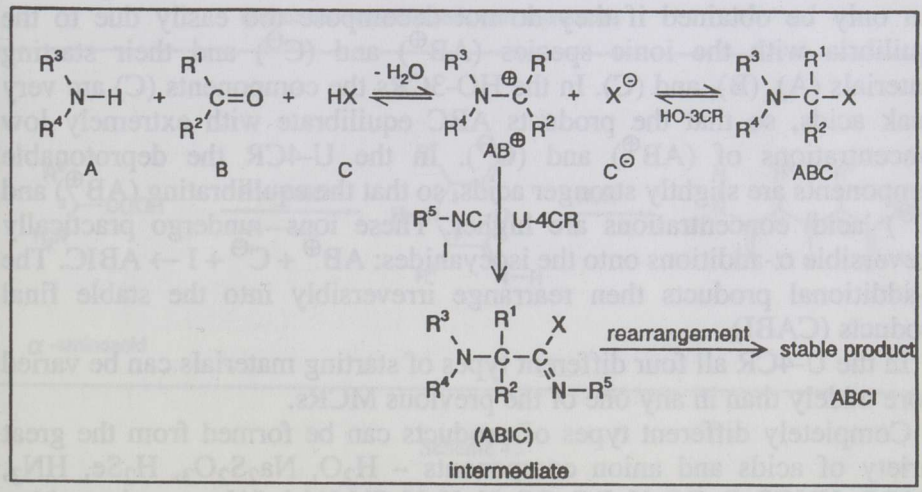
In 1971 *Isonitrile Chemistry*, edited by Ugi, was published together with the then most experienced authors in this field [11]. This seems to have provided the catalyst for the ensuing progress in the chemistry of isocyanides. Many new chemical reactions were developed and useful products prepared during the following decade [43], and even more so during the years that followed [44, 45].

During that time a number of new natural products were discovered in marine life by Scheuer et al. [46, 47]. Most of these are sequiterpene or diterpene derivatives with one or two isocyanide groups. One of these is a tri-isocyanide [46, 48]. A further class of naturally occurring cyclopentyl compounds was investigated by Baldwin et al. [49].

5. EARLY PROGRESS IN CHEMISTRY BY THE U-4CR

5.1. The essential features of the U-4CR

When isocyanides could be prepared conveniently and in sufficient yields (*Scheme 9*) [35b, 36, 42], an attempt was made to find new chemical reactions of isocyanides. Immediately, the 4CR of isocyanides, one of the most efficient preparative methods in syntheses, was discovered. It was realized that the essential relation of the P-3CR [11c], the HO-3CR [9], and the U-4CR corresponds to the equation P-3CR ∪ HO-3CR = U-4CR (*Scheme 10*), i.e. the U-4CR can be considered as a union [50] of the P-3CR and the HO-3CR.

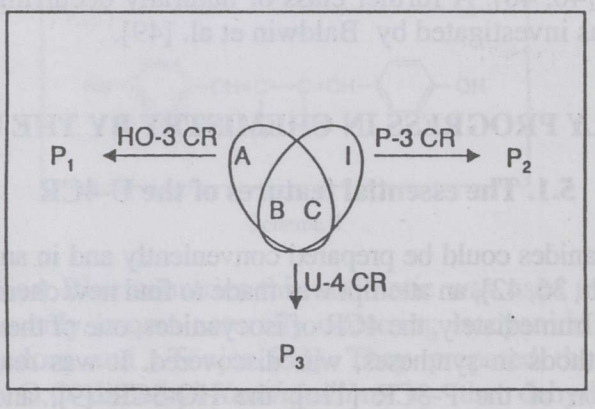


Scheme 10

The HO-3CR, a collection of the classical reactions and newer α-aminoalkylating reactions, involves α-additions of the cations ($AB^{\oplus}$), amines (A), and carbonyl compounds (B) together with the anions ($C^{\ominus}$) of weak acids (C) [9]. These name reactions already have great preparative advantages over the other usual chemical reactions in which only one or two chemical compounds react per step.

The P-3CR [11c, 30, 31] between carbonyl compounds (B), carboxylic acids (C), and isocyanides (I) is the only exception among the classical one-pot 3CRs. The reaction $B^{\oplus} + C^{\ominus} + I \rightarrow CIB \rightarrow CBI$ (*Scheme 7*) is a practically irreversible α-addition of a cation, an O-protonated carbonyl compound ($B^{\oplus}$) and an anion of a carboxylic acid ($C^{\ominus}$) onto the isocyanide (I). The exothermic process $C^{II} \rightarrow C^{IV}$ is the driving force for the entire reaction sequence.

The combination of both of these reactions led to the U-4CR of the isocyanides, a 4CR between amines (A), carbonyl compounds (B), acids (C), and isocyanides (I).



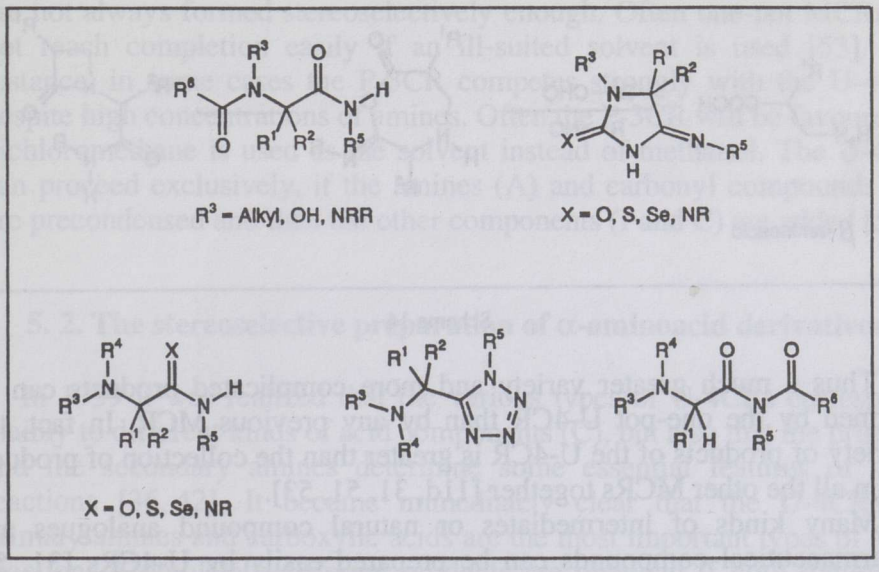
Scheme 11

In the collection of classical α-aminoalkylating HO-3CRs the products can only be obtained if they do not decompose too easily due to the equilibria with the ionic species ($AB^{\oplus}$) and ($C^{\ominus}$) and their starting materials (A), (B), and (C). In the HO-3CRs the components (C) are very weak acids, so that the products ABC equilibrate with extremely low concentrations of ($AB^{\oplus}$) and ($C^{\ominus}$). In the U-4CR the deprotonable components are slightly stronger acids, so that the equilibrating ($AB^{\oplus}$) and ($C^{\ominus}$) 'acid' concentrations are higher. These ions undergo practically irreversible α-additions onto the isocyanides: $AB^{\oplus} + C^{\ominus} + I \rightarrow ABIC$. The α-additional products then rearrange irreversibly into the stable final products (CABI).

In the U-4CR all four different types of starting materials can be varied more widely than in any one of the previous MCRs.

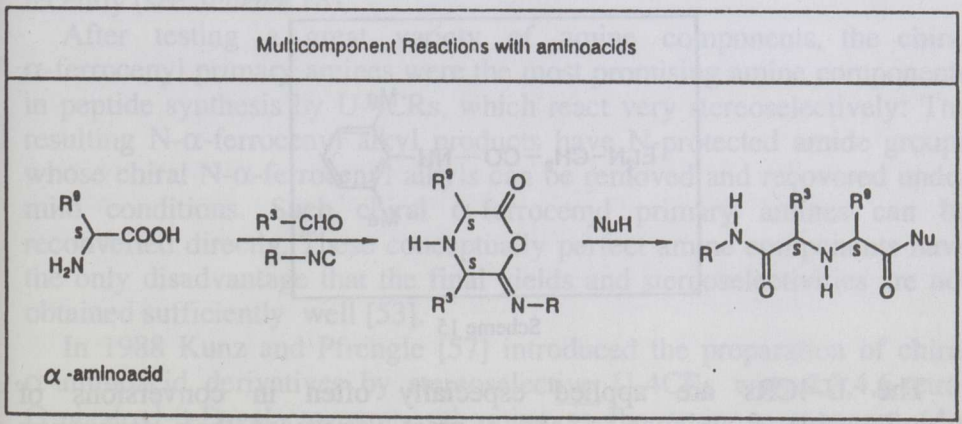
Completely different types of products can be formed from the great variety of acids and anion components – H_2O, $Na_2S_2O_3$, H_2Se, HN_3, HNCO, HNCS, R-CO_2H, RO-CO_2H, H_2N-CN [11d, 51] – together with a

variety of active nitrogen components like ammonia, primary amines hydroxylamine, and hydrazone on the one hand and secondary amines on the other hand. Anhydrous precondensed compounds between carbonyls and various nitrogen compounds have often advantages.

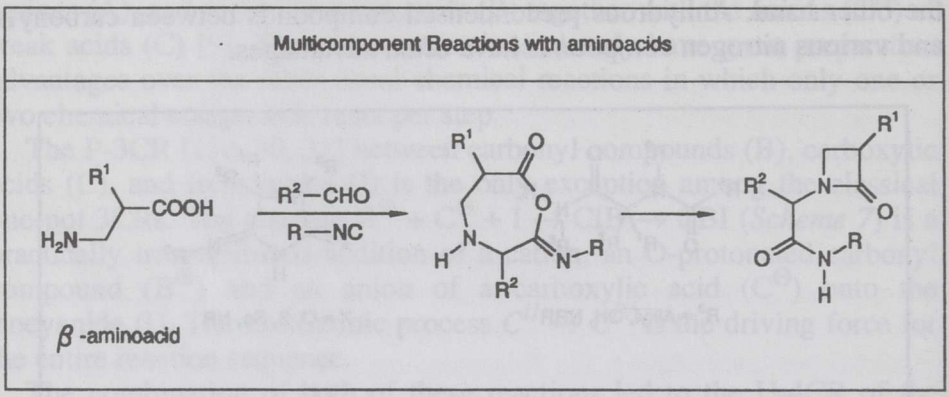


Scheme 12

Furthermore, in the U-4CR some of the starting materials can have two or three different functional groups, from which special types of products are formed [31]. For example, α-aminoalkyl acids (α-A–C) react with carbonyl compounds (B) and isocyanides (I) forming 1,1-iminodicarboxylic diacid derivatives (ABICD) [11g, 52], whereas with ß-aminoalkyl acids B and C are converted into ß-lactam derivatives (CABI) [11i, 53, 54].



Scheme 13



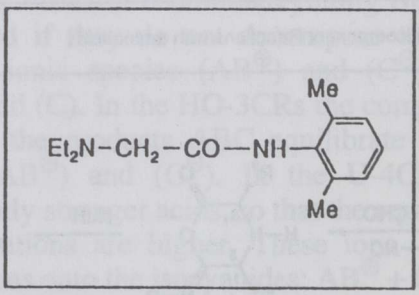
Scheme 14

Thus a much greater variety and more complicated products can be formed by the one-pot U-4CR than by any previous MCR. In fact, the variety of products of the U-4CR is greater than the collection of products from all the other MCRs together [11d, 31, 51, 53].

Many kinds of intermediates or natural compound analogues and pharmaceutical compounds can be prepared easily by U-4CRs [31, 53, 54]. In practically all cases fewer preparative steps are necessary and the yields of one-pot reactions are always higher than with multi-step procedures.

Joullié and her co-workers [55] are the pioneers in the development of new methods for the preparation of alkaloids and related chemical compounds by U-4CR chemistry.

One of the first attempts to apply the U-4CRs was made by the Swedish company AB Astra. It was preparation of *Xylocain*® [36], that is still one of the most widely used dental anaesthetics in the world.



Scheme 15

The U-4CRs are applied especially often in conversions of α-aminoacids, ß-aminoacids, and a great variety of their derivatives together with carbonyl compounds [31, 51, 53, 54].

Some U-5CRs are actually U-4CRs, forming intermediates that do not rearrange immediately into stable products, but combine further with

nucleophilic components (*Section 5. 2*). Until recently nobody was aware of the fact that some of the U-5CRs are real 5CRs, not just varieties of U-4CRs (*Section 6.1*).

There are many MCRs which result in rather low yields, because competing reactions may form undesired products, and chiral compounds are not always formed stereoselectively enough. Often one-pot MCRs do not reach completion easily if an ill-suited solvent is used [53]. For instance, in some cases the P-3CR competes strongly with the U-4CR, despite high concentrations of amines. Often the P-3CR will be favoured if dichloromethane is used as the solvent instead of methanol. The U-4CR can proceed exclusively, if the amines (A) and carbonyl compounds (B) are precondensed and then the other components (I and C) are added [53].

5. 2. The stereoselective preparation of α-aminoacid derivatives

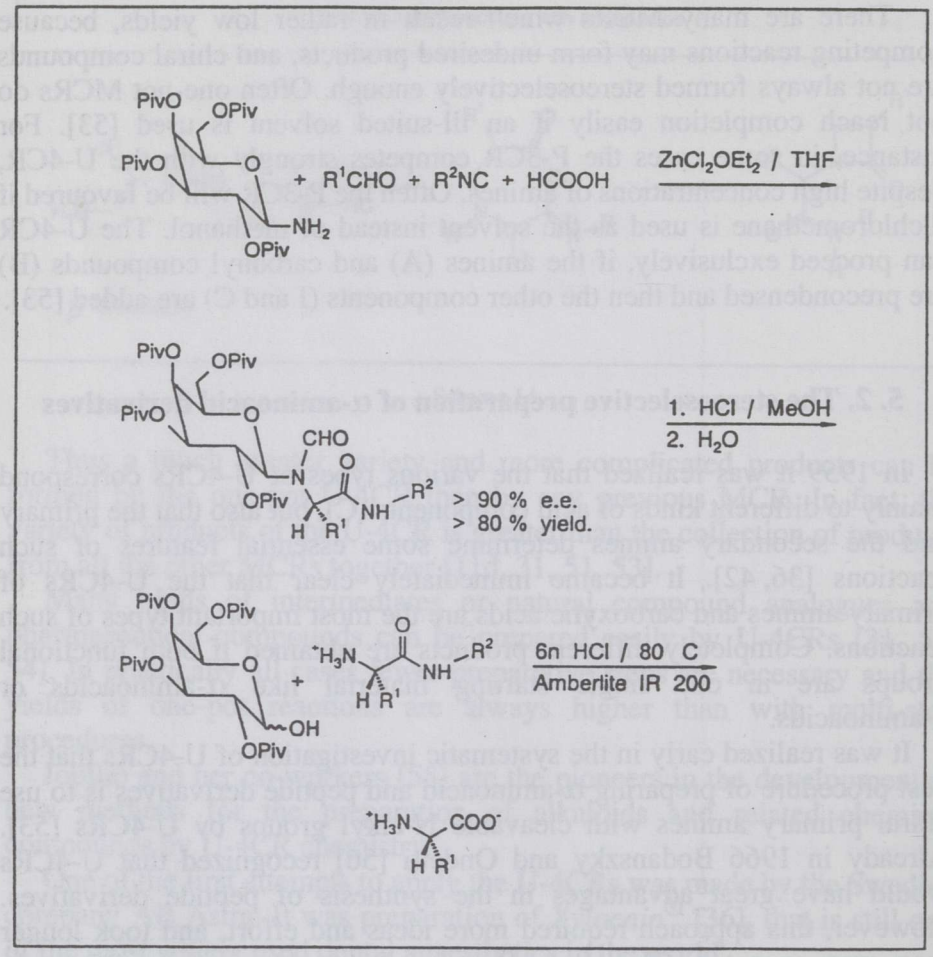
In 1959 it was realized that the various types of U-4CRs correspond mainly to different kinds of acid components (C), but also that the primary and the secondary amines determine some essential features of such reactions [36, 42]. It became immediately clear that the U-4CRs of primary amines and carboxylic acids are the most important types of such reactions. Completely different products are obtained if both functional groups are in one single starting material like α-aminoacids or ß-aminoacids.

It was realized early in the systematic investigation of U-4CRs that the best procedure of preparing α-aminoacid and peptide derivatives is to use chiral primary amines with cleavable N-alkyl groups by U-4CRs [53]. Already in 1966 Bodanszky and Ondetti [56] recognized that U-4CRs would have great advantages in the synthesis of peptide derivatives. However, this approach required more ideas and effort, and took longer than was expected. The desired approach has become possible only recently (see *Scheme 18*).

After testing a great variety of amine components, the chiral α-ferrocenyl primary amines were the most promising amine components in peptide synthesis by U-4CRs, which react very stereoselectively: The resulting N-α-ferrocenyl alkyl products have N-protected amide groups whose chiral N-α-ferrocenyl alkyls can be removed and recovered under mild conditions. Such chiral α-ferrocenyl primary amines can be reconverted directly. These conceptually perfect amine components have the only disadvantage that the final yields and stereoselectivities are not obtained sufficiently well [53].

In 1988 Kunz and Pfrengle [57] introduced the preparation of chiral α-aminoacid derivatives by stereoselective U-4CRs with 2,3,4,6-tetra-O-pivaloyl-ß-D-galacto-pyranosyl-amine as the amine component (A). There, only formic acid can be used as the acid component (C). Such U-4CRs proceed well in the presence of $ZnCl_2$ as a catalyst. The stereoselectivities and yields are generally excellent, and these chiral U-4CR prod-

ucts can be converted to the α-aminoacids by boiling them in hydrochloric acid.

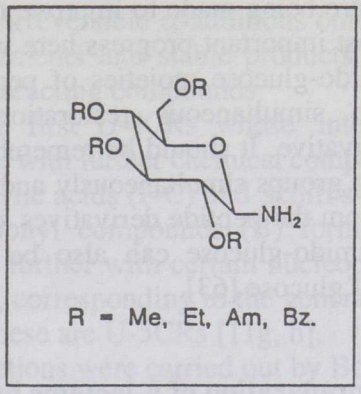


Scheme 16

This preparation of chiral α-aminoacids is a great improvement in comparison with previous methods with 10 and more steps and with low final yields [58].

However, only α-aminoacids and certain derivatives could be prepared by Kunz and Pfrengle by the U-4CR method, that cannot be extended into the synthesis of higher peptide derivatives using N-protected α-aminoacids (C) as their acid components.

In 1991 Goebel and Ugi [59] found that various α-aminoacids and peptide derivatives can be prepared by stereoselective U-4CRs from the 2,3,4,6-tetra-O-alkyl-ß-D-gluco-pyranosyl-amines (C). The N-alkylated O-alkylglucose moieties from such U-4CR products (ACIC) can be removed by TFA in the presence of thioanisole and various other compounds [60].

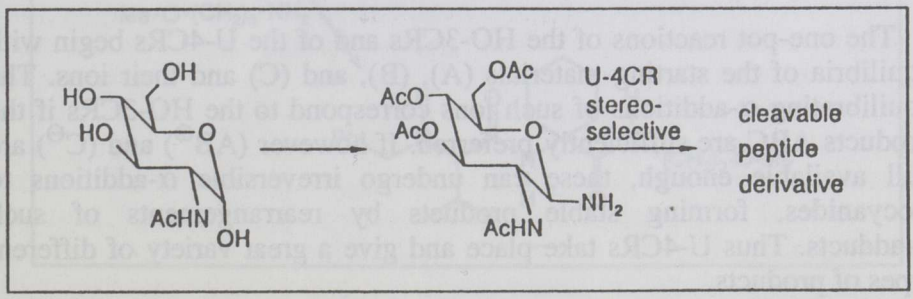


Scheme 17

Various natural products contain large amounts of 2-acetylamino-glucose.

In 1965 Marquarding and Ugi [53, 61] tested 2-aminoglucoses as components of U-4CRs. They observed that in methanol the mixture of 2-aminoglucose, benzoic acid, benzaldehyde, and tert-butyl isocyanide reacted at 0°C, and it was realized that this isocyanide was consumed completely. It was then hoped that some 2-glucosyl derivative could be obtained by the U-4CR, but only complex mixtures of many chemical products had formed, and no product could be isolated and characterized. These results were confirmed by Lehnhoff in 1993; he found that the mixtures underwent mainly P-3CRs instead of U-4CRs [62a]. 1-Amino-2-acetamido-glucose derivatives are probably the most effective amine reagents (A) in the preparation of α-aminoacids, peptides and their analogues by the U-4CR.

In the last few years the hitherto best method of preparing a great variety of α-aminoacids, peptides, and their derivatives [62] was found by using 1-amino-2-dioxy-2-N-acetyl-3,4,6-O-tri-ß-D-acetyl-glyco-pyranose as a chiral amine component of the U-4CR (A), together with carbonyl compounds (B), carboxylic acids, or N-protected α-aminoacids (C) and isocyanides, which may be α-isocyanoacid derivatives (I). The stereoselectivities of such U-4CRs are in most cases >99% d.e., and with only few exceptions, the yields are 80–90% pure products.

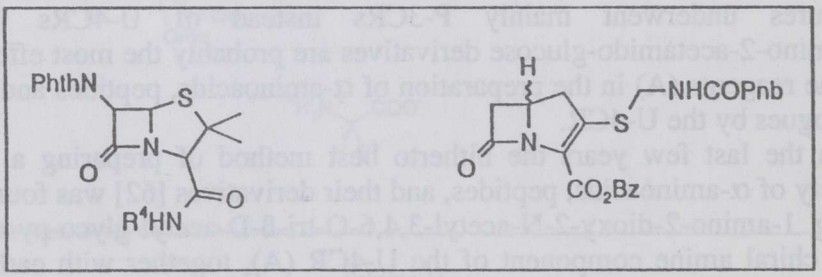


Scheme 18

Currently attempts are being made to improve the purity and yields of such products. The most important progress here would be to remove the N-protecting 2-acetamido-glucose moieties of peptide derivatives under mild conditions with simultaneous restoration of the 1-amino-2-acetamido-glucose derivative. It should be remembered that it is possible to remove N-protecting groups simultaneously and to re-synthesize chiral α-ferrocenyl amines from the peptide derivatives synthesized by U-4CRs [53, 58]. The 2-acetamido-glucose can also be easily converted into tetrazolyl derivatives of glucose [63].

5.3. The preparation of ß-lactams by U-4CRs

In 1957 Sheehan and Corey [64] described various ß-lactam syntheses requiring rather sophisticated methods. A few years later the preparation of ß-lactams became very simple: One of the earliest U-4CRs was the production of ß-lactams by mixing ß-aminoacids (A–C), carbonyl compounds (B), and isocyanides in a suitable solvent (*Scheme 14*) [65–67]. After the synthesis of some close analogues of penicillin [10i, 68–70] and cephalosporin [71], the preparation of a great variety of ß-lactam antibiotics and analogous compounds succeeded [54]. Several hundred such ß-lactam syntheses have been carried out in Switzerland, Japan, and the USA.



Scheme 19

5.4. Five-centred U-4CRs

The one-pot reactions of the HO-3CRs and of the U-4CRs begin with equilibria of the starting materials (A), (B), and (C) and their ions. The equilibrating α-additions of such ions correspond to the HO-3CRs if the products ABC are sufficiently preferred. If however ($AB^{\oplus}$) and ($C^{\ominus}$) are still available enough, these can undergo irreversible α-additions to isocyanides, forming stable products by rearrangements of such α-adducts. Thus U-4CRs take place and give a great variety of different types of products.

Many fundamentally different sequences of chemical reactions and their intermediates can take place in MCRs with ≥ 5 components. In all the

known higher MCRs, irreversible α-additions onto the isocyanides occur, followed by rearrangements into stable products, or by some secondary reactions with further reacting compounds.

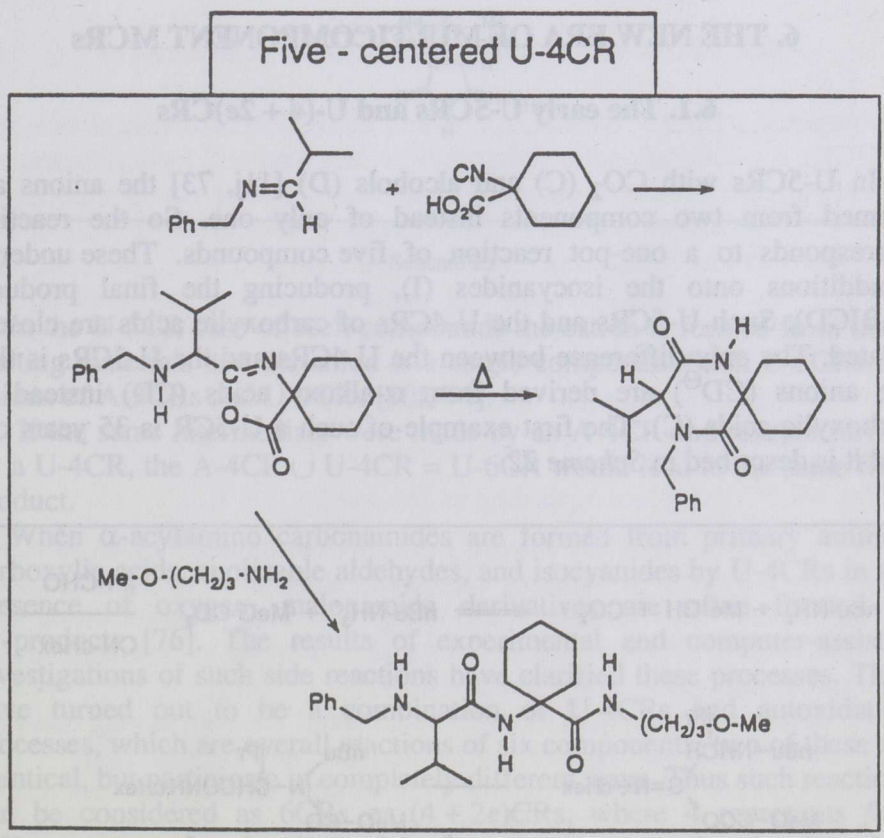
From 1967 on the first U-4CRs whose 'intermediate α-adducts' of isocyanides could react with further chemical compounds were carried out.

α-Isocyano carboxylic acids (I–C) and Schiff's bases (A–B) of primary amines (A) and carbonyl compounds (B) form five-membered cyclic products, which react further with certain nucleophiles (D) into a variety of peptide derivatives, corresponding to the general type of A–B + I–C → AB–IC → ABICD. These are U-5CRs [11g, h].

Recently such reactions were carried out by Bossio, Marcaccini, Paoli, and Pepino [45; see also 65–71].

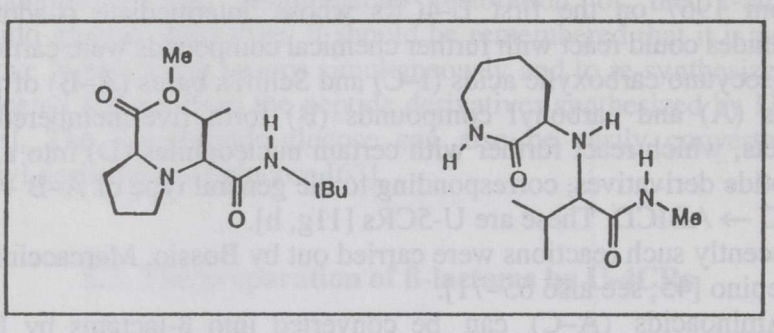
ß-Aminoacids (A–C) can be converted into ß-lactams by U-4CRs [65–71], whereas α-aminoacids do not form α-lactams analogously, but form 1,1-imino-dicarboxylic acid derivatives (*Schemes 13* and *14*).

Glycine, isobutyraldehyde, and cyclohexyl isocyanide form an achiral six-membered cyclic intermediate and this reacts further with methanol, producing the racemic 1,1-imino-dicarboxylic acid ester amide [11f].



Scheme 20

In the last few years it has been found that a great variety of chiral α-aminoacids react analogously by U-4CRs. These products are closely related to many biologically active natural products [72].



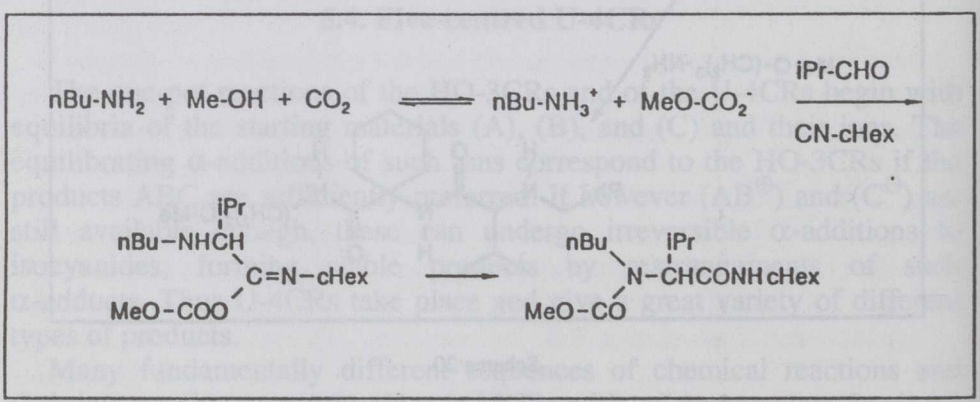
Scheme 21

Chiral 1,1'-imino-dicarboxylic acid methyl ester amide derivatives are prepared by five-centred U-4CRs. The components are just mixed together in methanol at 0–20°C and pure products are stereoselectively formed with ≥ 99% yields [72].

6. THE NEW ERA OF MULTICOMPONENT MCRs

6.1. The early U-5CRs and U-(4 + 2*e*)CRs

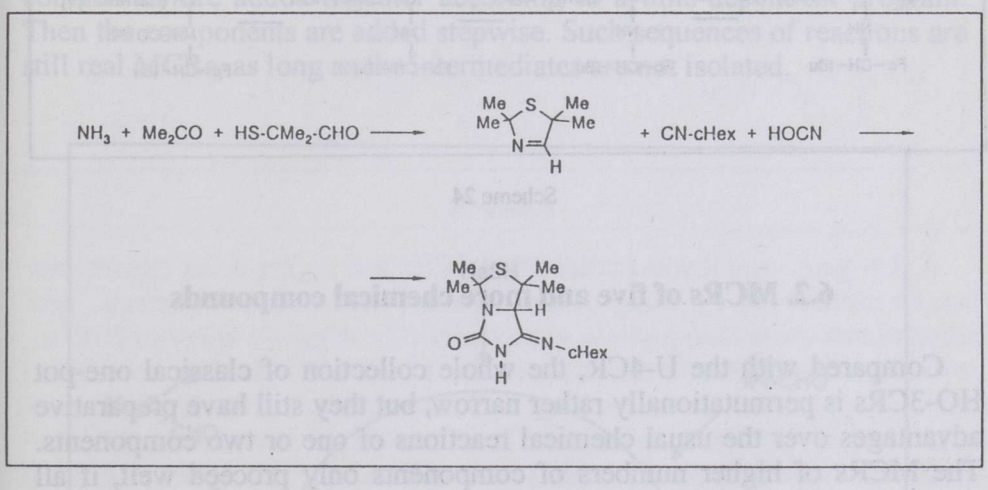
In U-5CRs with CO_2 (C) and alcohols (D) [11j, 73] the anions are formed from two components instead of only one. So the reaction corresponds to a one-pot reaction of five compounds. These undergo α-additions onto the isocyanides (I), producing the final products (ABICD). Such U-5CRs and the U-4CRs of carboxylic acids are closely related. The only difference between the U-4CRs and the U-5CRs is that the anions ($CD^{\ominus}$) are derived from α-alkoxy acids (CD) instead of carboxylic acids (C). The first example of such a U-5CR is 35 years old and it is described in *Scheme 22*.



Scheme 22

In these U-5CRs with CO_2 [11j] and alcohols, the anions are formed from two components instead of one, and so the reaction corresponds to a one-pot reaction of five compounds.

Another type of the U-5CR [11f, 74] was also found in the early period of U-4CRs. 2,2,4,4-Tetramethyl-Δ^3-thiazoline was reacted with cyanic acid and cyclohexyl-isocyanide, forming a bicyclic thiazoline derivative as the product. However, the reaction is not a typical U-4CR, as the reactive cation was not generated from two but three compounds by an A-3CR [22]. In further experiments ammonia, 2-mercapto-isobutyraldehyde, acetone, thiocyanic acid, and cyclohexyl isocyanide were reacted, and the same bicyclic thiazoline derivative was produced. Analogous U-5CRs can also be carried out with cyanates [75].



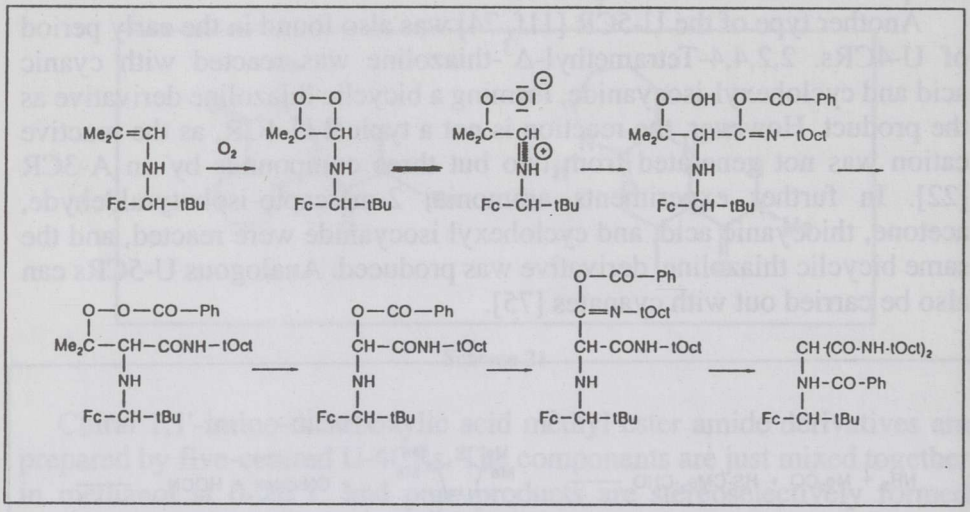
Scheme 23

In the U-5CR case of such compounds the cation is formed from three starting materials and the anion is a single compound. Such U-5CRs are unions of A-3CRs and U-4CRs [10f, 74].

If the same intermediate were made by an A-4CR and reacted further by a U-4CR, the A-4CR $\cup$ U-4CR = U-6CR would lead to the same final product.

When α-acylamino carbonamides are formed from primary amines, carboxylic acids, enolizable aldehydes, and isocyanides by U-4CRs in the presence of oxygen, malonamide derivatives are often formed as by-products [76]. The results of experimental and computer-assisted investigations of such side reactions have clarified these processes. They have turned out to be a combination of U-4CRs and autoxidation processes, which are overall reactions of six components; two of these are identical, but participate in completely different ways. Thus such reactions can be considered as 6CRs or $(4 + 2e)$CRs, where 4 represents *four different* types of molecules and $2e$ represents *two equal* molecules of an isocyanide. The details of such reactions (*Scheme 24*) were determined by preparative and computer-assisted chemistry [77]. The mathematically

based chemical computer program RAIN played an important role in the investigation [78–85].



Scheme 24

6.2. MCRs of five and more chemical compounds

Compared with the U-4CR, the whole collection of classical one-pot HO-3CRs is permutationally rather narrow, but they still have preparative advantages over the usual chemical reactions of one or two components. The MCRs of higher numbers of components only proceed well, if all compounds and intermediates, except the isocyanides, can equilibrate, and the final reaction steps toward the desired products are irreversible. Furthermore, no other irreversible reactions of isocyanides should compete with the desired MCRs. Often the MCRs proceed in better yields, if the components are not just mixed, but are added sequentially.

The first 7CR (*Scheme 25*) was reported in 1993 [86, 87].

This MCR takes place according to *Scheme 26*.

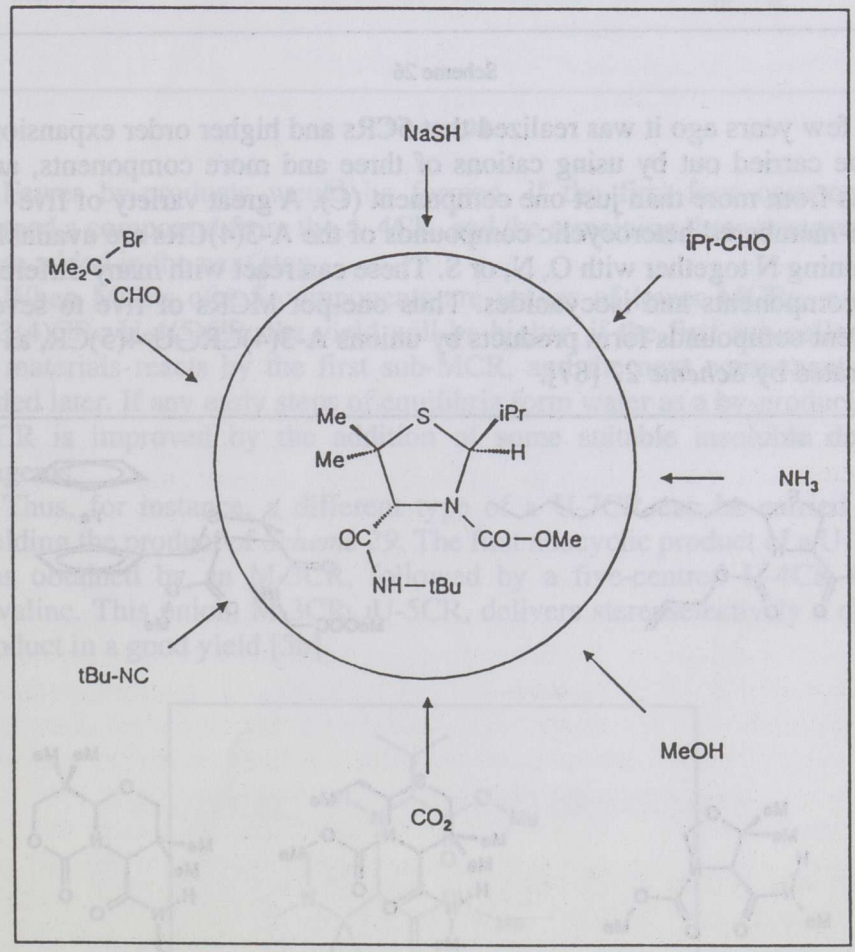
The 'α-amino cations' are formed from four components by an A-4CR, and the anions come of methoxy carboxylic acids from two components that equilibrate with methanol and CO_2. The anions and cations are subjected to an α-addition onto an isocyanide, followed by rearrangements into a stable final product in a yield of 43%.

The American and British journals wrote about 'a record among one-pot syntheses' [88] and 'raising this new technique to new heights' [89].

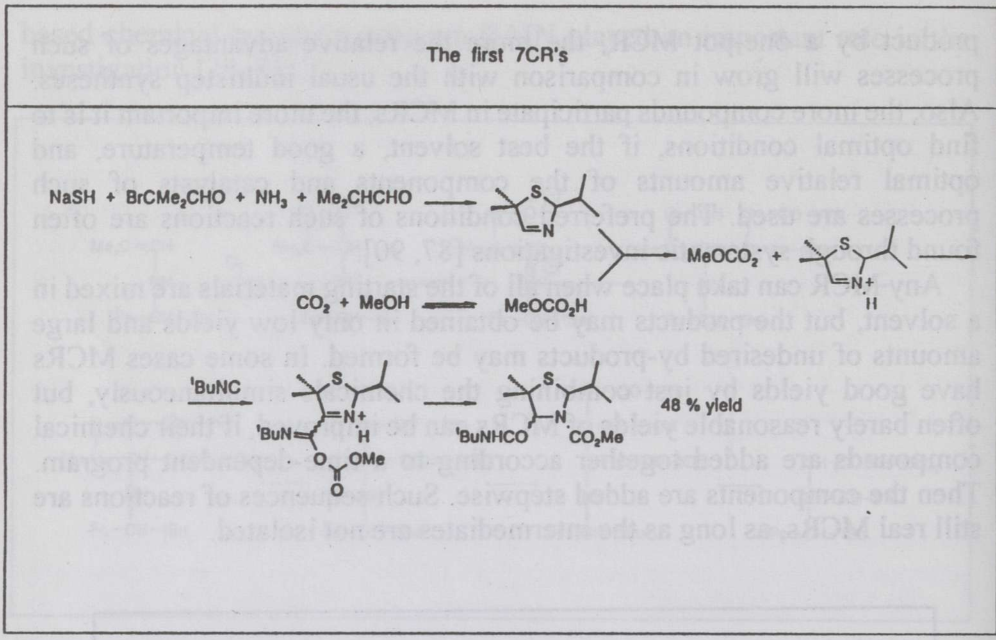
It was realized that this 7CR and a few similar reactions are not a few exceptional cases in chemistry, but that there is a wide variety of MCRs of five and more participating components, whenever one final practically irreversible reaction can take place. These can be α-additions to isocyanides reactions or followed by rearrangements that form stable five- or six-membered heterocyclic compounds. The more components form a

product by a one-pot MCR, the more the relative advantages of such processes will grow in comparison with the usual multistep syntheses. Also, the more compounds participate in MCRs, the more important it is to find optimal conditions, if the best solvent, a good temperature, and optimal relative amounts of the components and catalysts of such processes are used. The preferred conditions of such reactions are often found through systematic investigations [87, 90].

Any MCR can take place when all of the starting materials are mixed in a solvent, but the products may be obtained in only low yields and large amounts of undesired by-products may be formed. In some cases MCRs have good yields by just combining the chemicals simultaneously, but often barely reasonable yields of MCRs can be improved, if their chemical compounds are added together according to a time-dependent program. Then the components are added stepwise. Such sequences of reactions are still real MCRs, as long as the intermediates are not isolated.

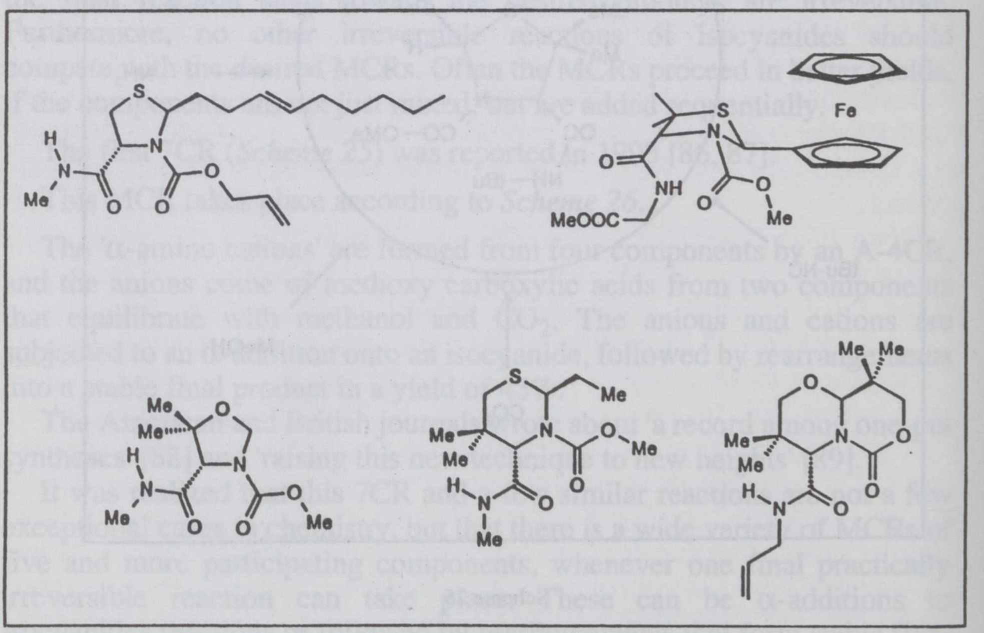


Scheme 25



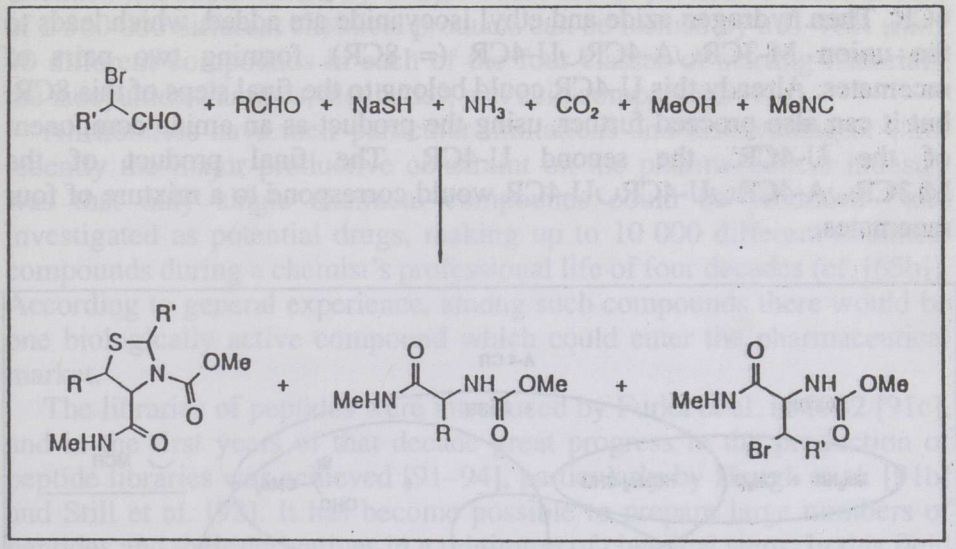
Scheme 26

A few years ago it was realized that 5CRs and higher order expansions can be carried out by using cations of three and more components, and anions from more than just one component (C). A great variety of five- to seven-membered heterocyclic compounds of the A-3(4)CRs are available, containing N together with O, N, or S. These can react with many different acid components and isocyanides. Thus one-pot MCRs of five to seven different compounds form products by unions A-3(4)CR∪U-4(5)CR, as is illustrated by *Scheme* 27 [87].



Scheme 27

The formation of by-products is illustrated in *Scheme 28* [87], where the main desired U-7CR product is accompanied by two U-5CR by-products.

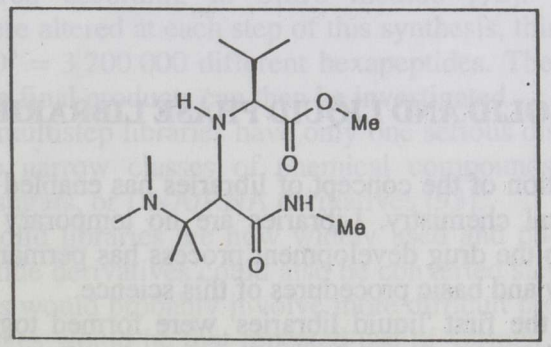


Scheme 28

Fewer by-products would be formed, if the first four components formed a compound from the A-4CR, and the remaining three components were added in the next step.

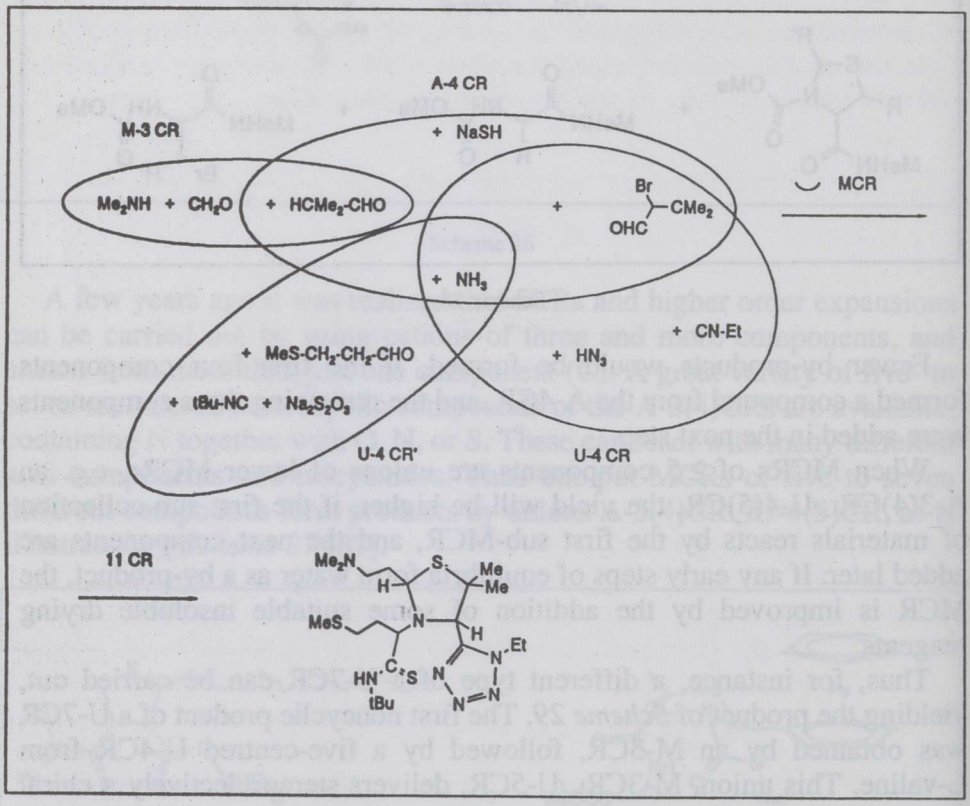
When MCRs of ≥ 5 components are unions of lower MCRs, e.g. an A-3(4)CR$\cup$U-4(5)CR, the yield will be higher, if the first sub-collection of materials reacts by the first sub-MCR, and the next components are added later. If any early steps of equilibria form water as a by-product, the MCR is improved by the addition of some suitable insoluble drying reagents.

Thus, for instance, a different type of a U-7CR can be carried out, yielding the product of *Scheme 29*. The first noncyclic product of a U-7CR was obtained by an M-3CR, followed by a five-centred U-4CR from L-valine. This union, M-3CR$\cup$U-5CR, delivers stereoselectively a chiral product in a good yield [5b].



Scheme 29

The 11CR of *Scheme 30* would probably proceed best, if it could be carried out stepwise. First the three components of the M-3CR would combine. In the next step, after adding three further reactants, the union M-3CR∪A-4CR (= 6CR) can form a racemic joint intermediate of this 6CR. Then hydrogen azide and ethyl isocyanide are added, which leads to the union M-3CR∪A-4CR∪U-4CR (= 8CR), forming two pairs of racemates. Already this U-4CR could belong to the final steps of this 8CR, but it can also proceed further, using the product as an amine component of the U-4CR', the second U-4CR. The final product of the M-3CR∪A-4CR∪U-4CR∪U-4CR would correspond to a mixture of four racemates.



Scheme 30

7. SOLID AND LIQUID PHASE LIBRARIES

The introduction of the concept of libraries has enabled great progress in pharmaceutical chemistry. Libraries are no temporary fashion: their introduction into the drug development process has permanently changed the methodology and basic procedures of this science.

Conceivably the first 'liquid libraries' were formed together with the first living cells, and from these libraries the first pure chemical

compounds were obtained subsequently by 'isolating' and localizing them during the development of life.

In 1961 the first *liquid library* was proposed [65b] in *Isonitrile Chemistry*, a book edited by I. Ugi. There it was postulated that a library of 2 560 000 different chemical products can be formed by a U-4CR using 40 different compounds in each of the four classes of starting materials, the isocyanides, amines, aldehydes, and acid components [11e].

All libraries have their particular limitations and disadvantages. Until recently the major productive constraint on the pharmaceutical industry was that only single chemical compounds could be produced and investigated as potential drugs, making up to 10 000 different chemical compounds during a chemist's professional life of four decades (cf. [65b]). According to general experience, among such compounds there would be one biologically active compound which could enter the pharmaceutical market.

The libraries of peptides were introduced by Furka et al. in 1982 [91c], and in the first years of that decade great progress in the production of peptide libraries was achieved [91–94], particularly by Hough et al. [91b] and Still et al. [92]. It has become possible to prepare large numbers of peptides and their derivatives in a minimum of chemical steps. In this field a great variety of elegant methods have been developed. Such peptide libraries have many advantages over the previous methods in special fields of pharmaceutical chemistry.

In recent years solid libraries, especially the combinatorial solid libraries of peptide derivatives, have represented great progress in certain areas of pharmaceutical chemistry. The immense efficiency of libraries is illustrated by an example of a peptide library of 117 649 different members [92].

A very simplified algebraic model of a solid peptide library is illustrated here. The first α-aminoacid is fixed to the polymer surface, which is divided into n_1 parts. Each one of these particles is combined with a different α-aminoacid derivative, forming n_1 dipeptides. Every surface part is divided into n_2 further parts and treated with n_2 different α-aminoacids. Thus $n_1 \cdot n_2$ different tripeptide derivatives are obtained, etc. Finally, $n_1 \cdot n_2 \cdot \ldots \cdot n_x$ individual peptide derivatives are produced, which are separated from the polymer surface. Hexapeptide libraries are usually prepared according to Still's method [92]. If 20 different aminoacids were altered at each step of this synthesis, this would produce a library of $20^5 = 3\,200\,000$ different hexapeptides. The pharmaceutical activities of the final products can then be investigated.

Such solid multistep libraries have only one serious disadvantage: they are limited to narrow classes of chemical compounds like the polypeptides, polysugars, or DNA/RNA derivatives [93].

Multistep solid libraries are now widely used and published [91–93]. The same peptide derivatives could also be converted stepwise in a liquid library, but this would probably involve more difficult procedures. One of the disadvantages would be that repeated use of various reagents and the removal of their by-products would be troublesome. Such an approach

would not have any preparative or pharmacological advantages. The products of such a liquid library cannot be separated, and the determination of the individual pharmacological properties of any of the compounds is not possible by conventional methods. Furthermore, in such liquid libraries of chemically similar compounds many products can also have similar pharmacological properties.

Recent progress was published by Carell et al. [94]. They described a very sophisticated liquid library of peptide derivatives.

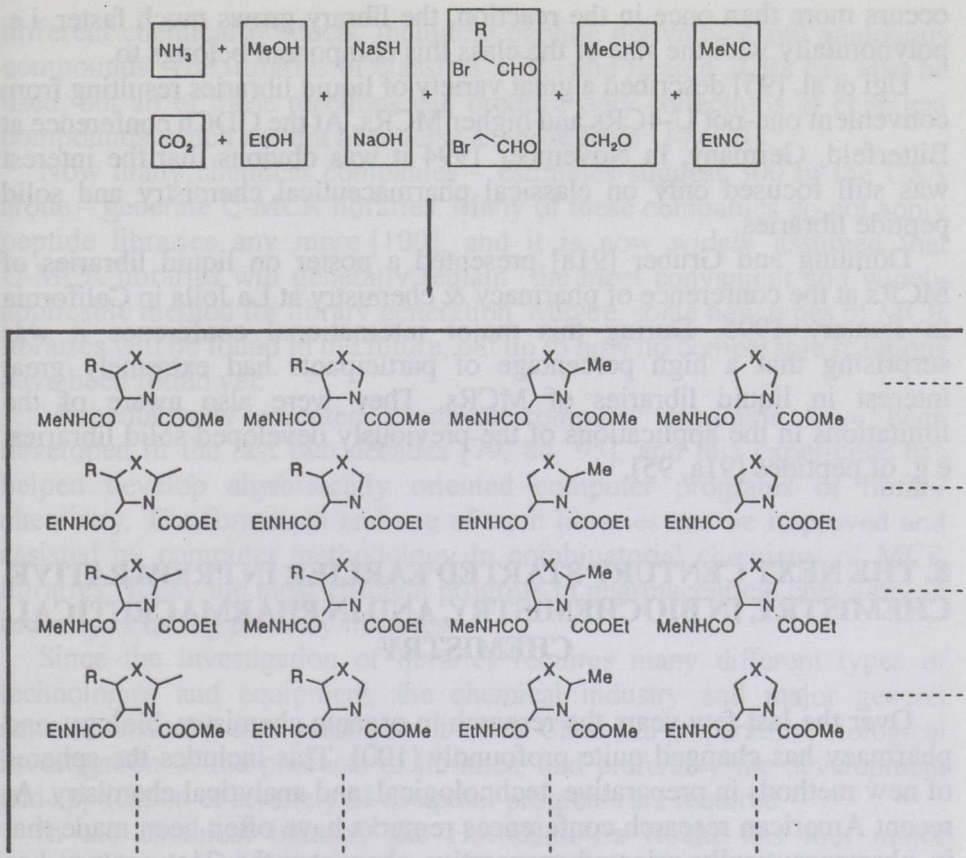
Recently solid and liquid one-pot MCR libraries were introduced [95]. The libraries of MCRs certainly have some limitations and disadvantages, in comparison to the now very popular and widely used solid libraries of multistep reactions of peptides [92]. However, MCR libraries have also a few advantages over the multistep libraries: The one-pot libraries of MCRs of n components are prepared in a single chemical step by just mixing all starting materials. In contrast, in multistep solid libraries of n components at least $n - 1$ chemical procedures must be carried out, and the left-over reagents and by-products must be removed at each step.

In the usual 3CRs, like in the M-3CR [13], a collection of only one general type of products can be prepared. The main advantage of U-MCR libraries is the possibility of preparing a much wider variety of chemical products. These are more dissimilar than those resulting from sequences of reactions between two components. If in the combinatorial libraries of MCRs maximal structural differences of the products are desired, their dissimilarity will grow with an increasing number of participating reactants. Such combinatorial MCR chemistry has completely changed the way how research is now done in the pharmaceutical industry.

On 3 April 1995 Armstrong [96] gave his lecture on 'Combinatorial libraries related to natural products' at the ACS National Meeting in Anaheim, California. There he presented solid libraries of 96 generally different U-4CRs. Those were formed from 1-cyclo-hexenyl isocyanide (I) [97], Merrifield amine beads (A) [98] together with widely variable aldehydes (B) and carboxylic acids (C) by his research group of the UCLS, Los Angeles, CA and the *Ontogen* company. These were among the first research groups that developed U-4CR solid libraries.

In 1993 Ugi's research group made a breakthrough in the investigation of MCR liquid libraries. For the first time U-MCRs were carried out with up to seven components [52, 86, 87, 95, 99]. In *Scheme 26* the liquid library comprises 144 individual chemical products resulting from two different components of all seven classes of starting materials. In these products 32 unequal chemical constitutions are contained, consisting of very many stereoisomers with one or two chiral centres [87].

Also new methods for the identification of chemical products with pharmacological properties in such liquid libraries were proposed and developed recently [52, 95, 99]. To the advantage of chemists, the participating compounds of molecular libraries are investigated simultaneously: If a liquid library as a whole has some pharmaceutical properties, then one knows that at least one of its products has this property.



Scheme 31

The next step is to partition the library, i.e. create sublibraries by excluding certain starting materials. The search for a positive product is done by logical exclusion and deduction: sublibraries can be produced by an MCR, leaving out some of the components. From half of the compounds of a class, such as the isocyanides, the size of the product library is also halved [91a]. Testing such sublibraries it can be deduced precisely which products, i.e. combinations of starting compounds, display the desired properties. The individual products can then be prepared selectively from the appropriate starting compounds by one-pot (American term: eintopf) MCRs.

We developed a new line of solutions for combinatorial chemistry and screening strategies, e.g. desktop software that manages combinatorial library data. This software solves one of the biggest problems faced by laboratories doing combinatorial chemistry: managing the enormous volume of data generated. Structures can be effectively and efficiently stored as libraries, and retrieved as specific structures when needed. It enables chemists to plan their combinatorial syntheses, one of the most time-consuming steps in the combinatorial process.

The size of libraries is determined by the number of reacting educts. In general, for an *n*-component reaction with *n* different classes of educts the library grows linearly with the size of each class. When a component

occurs more than once in the reaction, the library grows much faster, i.e. polynomially with the size of the class this component belongs to.

Ugi et al. [95] described a great variety of liquid libraries resulting from convenient one-pot U-4CRs and higher MCRs. At the GDCh conference at Bitterfeld, Germany, in November 1994 it was obvious that the interest was still focused only on classical pharmaceutical chemistry and solid peptide libraries.

Dömling and Gruber [91a] presented a poster on liquid libraries of MCRs at the conference of pharmacy & chemistry at La Jolla in California in January 1995. During this major international conference it was surprising that a high percentage of participants had extremely great interest in liquid libraries of MCRs. They were also aware of the limitations in the applications of the previously developed solid libraries, e.g. of peptides [91a, 95].

8. THE NEXT CENTURY STARTED EARLIER IN PREPARATIVE CHEMISTRY, IN BIOCHEMISTRY, AND IN PHARMACEUTICAL CHEMISTRY

Over the last few years the research in organic chemistry, biology, and pharmacy has changed quite profoundly [100]. This includes the spheres of new methods in preparative, technological, and analytical chemistry. At recent American research conferences remarks have often been made that in pharmaceutically oriented preparative chemistry the 21st century has already started.

The progress of various types of research has been quick and profound. Some areas have changed gradually, so that this has not been recognized immediately. In various other fields, the progress has occurred quite recently and almost suddenly. It seems that just during the last few months a new combination of scientific methods has changed a major field of science [100]. This progress is not due to just one single new scientific result, method, or technology, but it is due to a great variety of developments in the ways of reasoning and fast progress in experimental approaches.

In the last decade the libraries of peptides, like the ubiquitous hexapeptide libraries, and DNA/RNAs became scientifically fashionable. However, in 1994 an increasing number of industrially oriented scientists realized that the libraries of such chemical products cannot be structurally and stereochemically sufficiently different to meet the needs of pharmaceutical chemistry.

The new methods of preparing isocyanides and the introduction of the U-4(5)CR started almost four decades ago, and recently U-MCRs of even higher numbers of different compounds have been developed. It has been realized that one-pot U-MCR libraries are now almost ideal procedures in pharmaceutical chemistry, since such reactions allow the chemist to produce an extremely wide variety of structurally and stereochemically

different chemical products, including peptide derivatives and analogous compounds. The libraries of classical 3CRs and related 3CRs can also be used, but all of these reactions can produce only collections of chemical compounds which are not as diverse as those from U-MCRs.

Now many chemical companies – estimates suggest 500 in the USA alone – generate U-MCR libraries. Many of these companies do not apply peptide libraries any more [100], and it is now widely assumed that U-MCR libraries will generally remain the most convenient and widely applicable method for library generation. Maybe, some new types of MCR libraries will be found in the future, but up to now no comparable reactions have been found yet.

Mathematically oriented chemical computer programs have been developed in the last two decades [79, 84, 95], and this experience has helped develop algebraically oriented computer programs of library chemistry. The formation and use of such libraries can be improved and assisted by computer methodology in combinatorial chemistry of MCR libraries. Today the most efficient progress in pharmaceutical chemistry in industry is taking place by libraries.

Since the investigation of libraries requires many different types of technologies and equipment, the chemical industry and major general research institutes can investigate libraries. Chemical preparation, biological investigation of the products of libraries, and preferably the development and application of a variety of computer programs are required.

In the chemical industry the Hoffmann–La Roche has four major organizations doing library research, and in May 1995 this company decided to publish some of the progress in library chemistry they have made. It is now well known that small molecules are pharmaceutically preferred to large ones.

In the pharmaceutical industry the libraries of U-4CR and higher U-MCRs are favoured nowadays, since a wide variety of pure and stable products can be made in high quantities by a one-pot MCR in a single reactive step.

The libraries of biologically active peptides and DNA/RNA derivatives are made up of rather large molecules that are produced by the usual methods in very many preparative steps. Therefore, fewer libraries of these compounds are produced and investigated.

The U-MCRs allow the chemist to produce an extremely wide variety of very different types of products, whereas each other MCR produces only similar products of the same type.

The co-workers of I. Ugi have developed three types of mathematically oriented computer programs. One of these will help decide the choice of starting materials in liquid and solid libraries. Other computer programs will organize the application of organic libraries, and still others will calculate the minimal number of experiments in finding individual biologically active compounds.

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 more based on computer-oriented automatic devices. Scientists will be needed more in understanding and in planning and designing chemical reasoning than in practical production.

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REFERENCES

1. Posner, G. H. Multicomponent one-pot annulations of three to six bonds. – Chem. Rev., 1986, **86**, 831–844; Michael, J. P., Pattenden, G. Marine Metaboliten und die Komplexierung von Metall-Ionen: Tatsachen und Hypothesen. – Angew. Chem., 1993, **105**, 1–24; Angew. Chem. Int. Ed. Engl., 1993, **32**, 1–23; Tietze, L. F., Beifuss, U. Sequentielle Transformationen in der Organischen Chemie – eine Synthesestrategie mit Zukunft. – Angew. Chem., 1993, **105**, 137–170; Angew. Chem. Int. Ed. Engl., 1993, **32**, 131–163.
2. Heathcock, C. H. Die Fascinierenden Alkaloide aus Yuzuriha. – Angew. Chem., 1992, **104**, 675–691; Angew. Chem. Int. Ed. Engl., 1992, **31**, 665–708.
3. March, J. Advanced Organic Chemistry. J. Wiley & Sons, New York, 1985.
4. Woodward, R. B., Cava, M. P., Ollis, W. D., Hunger, A., Daeniker, H. U., Schenker, K. Strychnine! – J. Am. Chem. Soc., 1954, **76**, 4749–4751; The total synthesis of strychnine. – Tetrahedron, 1963, **19**, 247–288.
5. Ugi, I., Dömling, A., Hörl, W. a) Multicomponent reactions in organic chemistry. – Endeavour (Oxford), 1994, **18**, 3, 115–122; b) Multikomponentenreaktionen. – GIT Fachzeitschrift für das Laboratorium, 1994, **38**, 430–437; c) Ugi, I., Dömling, A., Göbel, M., Hörl, W., Kehagia, K., Lehnhoff, S., Starnecker, M. Flerkomponentsreaktioner gernya läkemedel. – Kemisk Tidskrift (Sweden), 1995, **107**, 4, 50–52.
6. Knight, S. D., Overman, L. E., Paerudeau, G. Enantioselective total synthesis of (-)-strychnine. – J. Am. Chem. Soc., 1993, **115**, 9293–9294.
7. Beifuss, U. Die Totalsynthese von (-)-Strychnin. – Angew. Chem., 1994, **106**, 1204–1209; Angew. Chem. Int. Ed. Engl., 1994, **33**, 1187–1192.
8. Hjelt, E. Geschichte der Organischen Chemie. Vieweg & Söhne, Braunschweig, 1916.
9. Hellmann, H., Opitz, G. α-Aminoalkylierung. Verlag Chemie, Weinheim, 1960.
10. Ugi, I., Kaufhold, G. Stereoselektive Synthesen IV. Der Reaktionsmechanismus stereoselektiver Vierkomponentenkondensationen. – Liebigs Ann. Chem., 1967, **709**, 11–28.
11. Ugi, I. Isonitrile Chemistry. Academic Press, New York, 1971, Vol. 20; a) p. 1; b) p. 9; c) p. 133; d) p. 145; e) p. 149; f) p. 152; g) p. 158; h) p. 159; i) p. 181; j) p. 185; k) p. 186; l) p. 201.
12. Strecker, A. Bildung von Cyanaminen aus Aldehyden. – Ann. Chem., 1850, **75**, 27–34.
13. Mannich, C., Krösche, I. Aminalkylierungen von Ketonen. – Arch. Pharm., 1912, **250**, 647–659; Blick, F. F. Organic Reactions. Ed. R. Adams. Vol. 1. John Wiley & Sons, New York, 1942, 303–341.

14. Robinson, R. The synthesis of tropinone. – J. Chem. Soc., 1917, (II), 762–768.
15. Schöpf, C., Lehmann, G., Arnold, W. Synthese von Naturstoffen, insbesondere von Alkaloiden, unter physiologischen Bedingungen für die Frage der Entstehungs einiger pflanzlichen Naturstoffe in der Zelle. – Angew. Chem., 1937, **50**, 779–803; Arnold, W. The preparation of alkaloids and similar compounds under physiological conditions. – Endeavour (Oxford), 1986, **107**, 10–18.
16. Lindsay, J. K., Hauser, G. R. Aminomethylation of ferrocene to N,N-dimethylferrocene and its conversion into corresponding alcohols and aldehyde. – J. Org. Chem., 1957, **22**, 355–358.
17. Herrmann, R. Synthese von α-Ferrocenylverbindungen. Doctoral Thesis, Techn. Univ. München, D-85747 Garching, 1981; Herrmann, R., Ugi, I. The electrophilic substitution of ferrocene by protonated carbonyl compounds. – Tetrahedron, 1981, **37**, 1001–1009.
18. Wagner, G., Herrmann, R. Ferrocenes. Eds. A. Togni, T. Hayashi. VCH, Weinheim, 1995.
19. Hantzsch, A. Die Bildungsweise von Pyrrolderivaten. – Ber. Dtsch. Chem. Ges., 1890, **23**, 1474–1476.
20. Bignelli, P. Reactioni Heterocyclici. – Gaz. Chim. Ital., 1893, **23**, 360–367.
21. Bergs, H. Hydantoinderivate. Ger. Pat. 1929, 566094; Chem. Abstr., 1933, **27**, 1001; Bucherer, T., Steiner, W. Über die Reaktionen der α-Oxy und α-Aminonitrilen. Synthese von Hydantoinen. – J. Prakt. Chem., 1934, **140**, 291–316; Bucherer, H. T., Lieb, V. A. Über die Bildung substituiereter Hydantoine aus Aldehyden und Ketonen. – Ibid., 1934, **141**, 5–43.
22. Asinger, F. Über die gemeinsame Einwirkung von Schwefel und Ammoniak auf Ketone. – Angew. Chem., 1956, **68**, 413; Asinger, F., Thiel, M., Pallas, E. Die gemeinsame Einwirkung von Schwefel und Ammoniak auf Diäthylketone. – Liebigs Ann. Chem., 1957, **602**, 37–49; Asinger, F., Thiel, M. – Angew. Chem., 1958, **70**, 667–683; Asinger, F., Offermanns, H. Synthese von Ketonen, Schwefel und Ammoniak oder Aminen bei Raumtemperatur. – Angew. Chem., 1967, **79**, 953–965; Angew. Chem. Int. Ed. Engl., 1967, **6**, 907–927; Asinger, F., Leuchtenberg, W., Offermanns, H. Schwefelhaltige Heterocyclen durch Umsetzung von Ketonen, Schwefel und Ammoniak bzw. Amine. – Chem. Zeitung, 1974, **94**, 610–615; Asinger, F., Gluzek, K. H. – Monats. Chem., 1983, **114**, 47–63.
23. Dömling, A., Ugi, I. K. A new 5,6-dihydro-2*H*-1,3-oxazine synthesis via Asinger-type condensation. – Tetrahedron, 1993, **49**, 9499–9500.
24. Lieke, W. Die Reaktion von Cyansilber und Jodkohlenwasserstoff. – Justus Liebigs Ann. Chem., 1859, **112**, 316–321.
25. Meyer, E. Neue Versuche mit Cyansilber. – J. Prakt. Chem., 1866, [1] **67**, 147–155.
26. Gautier, A. Les réactiones des amines. – Justus Liebigs Ann. Chem., 1867, **142**, 289–297.
27. Hofmann, A. W. Über die aromatischen Cyanate. – Ber. Dtsch. Chem. Ges., 1870, **3**, 653–666.
28. Nef, I. U. Übersicht über das Zweiwertge Kohlenstoffatom. – Justus Liebigs Ann. Chem., 1892, **270**, 267–335; Verhältnis der Alkaloide gegen alkoholische Kalibezw. Natriumalkoholate. – Justus Liebigs Ann. Chem., 1899, **309**, 126–189.
29. Oliveri-Mandala, E., Alagna, B. Reazioni con isonitrili e azidi. – Gazz. Chim. Ital., 1910, **40 II**, 441–448.
30. Passerini, M. Sopra gli isonitrili (I). Composto del p-isonitrili-azobenzolo con acetone ed acido acetica. – Gazz. Chim. Ital., 1921, **51 II**, 126–129; Sopra gli isonitrili (II). Composti con aldehidi o con chetonied acidi organici monobasici. – Ibid., 181–188; Sopra gli isonitrili XV. Reazoni con gli isonitrili alifatici. – Ibid., 1926, **56**, 826; Passerini, M., Ragni, G. Sopra gli isonitrili. – XIX Reazoni con acidi aldehidici e chetonoci. – Ibid., 1931, **61**, 964–969.
31. Ugi, I., Lohberger, S., Karl, R. The Passerini and Ugi reactions. – In: Trost, B. M., Heathcock, C. H. (eds.). Comprehensive Organic Chemistry: Selectivity for Synthesis Efficiency. Vol. 2, Pergamon, Oxford, 1991, 1083–1109, a) p. 1090.
32. Rothe, W. Wirkung des *Penicillium notatum*. – Pharmazie, 1950, **5**, 190–197.
33. Hagedorn, I., Tönjes, H. Die Herstellung eines Diisocyanids durch Wasserabspaltung Diformylamins mittels Phenylsulfonylchlorid in Anwesenheit des Pyridins. – Pharmazie, 1956, **11**, 409–416; Die Herstellung O,O'-Dimethyl-Xanthocillin. – Ibid., 1957, **12**, 567–572.
34. Achenbach, H., Grisebach, H. – Naturforschung, 1965, **20 b**, 137–143.

35. a) Ugi, I., Meyr, R. Neue Darstellungsmethode für Isonitril. – Angew. Chem., 1958, **70**, 702–703; b) Obrecht, R., Hermann, R., Ugi, I. Isocyanide syntheses with phosphoroxychloride and diisopropylamine. – Synthesis, 1985, 400–402.
36. Ugi, I. Neuere Methoden der präparativen organischen Chemie IV. Mit Sekundärreaktionen gekoppelte α-Additionen von Immonium-Ionen und Anionen an Isonitrile. – Angew. Chem., 1962, **74**, 9–22; Angew. Chem. Int. Ed. Engl., 1962, **1**, 8–21.
37. Ugi, I., Fetzer, U., Eholzer, U., Knupfer, H., Offermann, K. Neuere Methoden der präparativen organischen Chemie IV. Isonitril-Synthesen. – Angew. Chem., 1965, **77**, 492–494; Angew. Chem. Int. Ed. Engl., 1965, **4**, 472–482.
38. Skorna, G., Ugi, I. Isonitril-Synthese mit Diphosgen. – Angew. Chem., 1977, **9**, 267; Angew. Chem. Int. Ed. Engl., 1977, **16**, 259.
39. Eckert, H., Forster, B. Ein kristalliner Phosgen Ersatz. – Angew. Chem., 1987, **99**, 922–923; Angew. Chem. Int. Ed. Engl., 1987, **26**, 1221–1223.
40. Hertler, W. R., Corey, E. J. Novel preparation of isocyanides. – J. Org. Chem., 1958, **23**, 1221–1222.
41. Skorna, G., Ugi, I. Bifunktionelle Isocyanide als Reagenzien zur Einführung von Isocyangruppen in Polystyrol-Divinylbenzol Copolymere. – Chem. Ber., 1978, **111**, 3965–3968; Arshady, R., Ugi, I. Solid phase peptide synthesis by four component condensation; Peptide formation on an isocyano polymer support. – Z. Naturforschung, 1981, **36b**, 1202–1203; Synthese makromolekularer Isocyanide mit allgemeiner Lösungsmittelverträglichkeit – Neuartige Polymerträger für Festphasensynthesen. – Angew. Chem., 1982, **94**, 367; Angew. Chem. Int. Ed. Engl., 1982, **21**, 374; Angew. Chem. Suppl., 1982, 761–768; Synthesis and characterization of polymer supports carrying isocyano groups. – Polymer, 1990, **31**, 1164–1169.
42. Ugi, I., Meyr, R., Fetzer, U., Steinbrückner, C. Versuche mit Isonitrilen. – Angew. Chem., 1959, **71**, 386.
43. e. g.: van Leusen, A. M., Siderius, H., Hoogenboom, B. E., van Leusen, D. A new and simple synthesis of the pyrrole system from Michael acceptors and tosylmethylisocyanide. – Tetrahedron Lett., 1972, **13**, 5337–5340; Saegusa, T., Ito, Y. Synthesis of cyclic compounds via copper–isonitrile complexes. – Synthesis, 1975, 291–300; Eckert, H. Einführung von schonend abspaltenden Carboxyl-Schutzgruppen mittels der Passeri-Reaktion. – Ibid., 1977, 332–333; Schöllkopf, U. α-Metalated isocyanides in organic synthesis. – Pure & Appl. Chem., 1979, **51**, 1347–1355; Neuere Anwendungen α-Metallierter Isocyaniden der organischen Synthese. – Angew. Chem., 1977, **89**, 351–360; Angew. Chem. Int. Ed. Engl., 1977, **16**, 339–348; Walborsky, H. M., Perasamy, M. P. Isocyanides in the organic synthesis. Review. – Org. Prep. Prac. Int., 1979, **11**, 293–296; Ito, Y., Kazuhira, K., Kato, H. Reaction of o-tolyl. Isocyanide and isothiocyanates. – Tetrahedron Lett., 1979, 1039–1042; Ito, Y., Saegusa, T. Reaction of o-tolylisocyanide with isocyanate and isothiocyanate – syntheses of N-substituted indole-3-carboxamides and indole-3-thiocarboxamides; Ito, Y., Kato, K., Imai, H., Saegusa, T. A novel conjugation hydrocyanation with $TiCl_4$-tert-butyl isocyanate. – J. Am. Chem. Soc., 1982, **104**, 6449–6450; Ito, Y., Kobayashi, Y. I., Seco, N., Saegusa, T. Indole synthesis utilising o-methyl-phenyl isocyanide. – Bull. Chem. Soc. (Japan), 1984, **57**, 73–84; Ito, Y., Imai, H., Kato, K., Segar, H., Saegusa, T. Cyanates of acetals and t.-butyl isocyanide – $TiCl_4$. – Chem. Lett., 1984, 937–940.
44. van Leusen, D., Flentge, E., van Leusen, A. M. An efficient synthesis of 3-nitropyroles. – Tetrahedron, 1991, **47**, 4639–4644; van Leusen, D., van Echten, E., van Leusen, A. M. Electron-withdrawing and/or electron-donating nature; Bossio, R., Marcaccini, S., Paoli P., Papalea, S., Pepino, R., Polo, C. Studies in isocyanides and related compounds – synthesis and cyclizations of N-substituted 1-isocyano-1-cycloalkenecarboxamides. – Liebigs Ann. Chem., 1991, 843–849; Bossio, R., Marcaccini, S., Padi, P., Pepino, R., Polo, C. Studies of isocyanide and related compounds – synthesis of cyclization of N-substituted 1-isocyano-1-cycloalkanecarboxamides. – Synthesis, 1991, 999; Stoelwinder, J., von Zoest, W., van Leusen, A. M. Chemistry of N,P-acetals: Application to the synthesis of 20-ketosteroids. – J. Org. Chem., 1992, **57**, 2249–2252; Murakami, M., Kawano, T., Ito, H., Ito, Y. Synthesis of α-hydroxy ketone by samarium

(II) iodide, and carbonyl compounds. – J. Org. Chem., 1993, **58**, 1458–1465; Fehlhammer, W. P., Rieder, D., Lotz, S., Kernbach, U., Fuchs, J. Dreikomponenten-cycloaddition mit Cyankomplexen. – Chem. Ber., 1993, **126**, 2243–2246; Anorg. Chim. Acta, 1994, **222**, 275–282; Bossio, R., Marcaccini, S., Pepino, R. Isocyanides and related compounds: A novel synthesis of pyrroles via Ugi reaction. – Synthesis, 1994, 765–766.

45. Bossio, R., Marcaccini, S., Paoli, P., Pepino, R. Synthesis of N,N'-diaryldipeptide amide by multi-component condensation utilizing potassium isocyanoacetate. – Synthesis, 1994, 672–674.
46. Chang, C. W. J., Scheuer, P. J. Isocyanides in nature. – Top. Can. Chem., 1993, **167**, 33–75.
47. Scheuer, P. J. Isocyanides and cyanides as natural products. – Acc. Chem. Res., 1992, **25**, 433–439.
48. Patra, A., Chang, C. W. J., Scheuer, P. J. An unprecedented *Trusoajjana diterpenoid* antibiotic from a sponge. – Am. Chem. Soc., 1984, **106**, 7981–7983.
49. Baldwin, J. E., Aldinger, R. M., Chandragiamu, J., Edenbarough, M. S., Keeping, J. W., Ziegler, C. B. Structure and synthesis of new cyclopentyl isonitriles from *Trichodetma hamatum* (Bon.) Bain agor HLX 1379. – J. Chem. Soc. Chem. Comm., 1985, 816–817.
50. MacLane, S., Birkhoff, G. Algebra. MacMillan Limited, New York, 1967 [p. 3.: Given sets of R and S have the *intersection* $R \cap S$ with the common elements R and S. This means $R \cap S = \{ x \mid x \in R \text{ and } x \in s \}$, whereas a union $R \cup S$ is $R \cup S = \{ x \mid x \in R \text{ or } x \in s \}$].
51. Ugi, I. Von Isocyaniden via Vierkomponentenkondensationen zu Antibiotika-Synthesen. – Angew. Chem., 1982, **94**, 826–835; Angew. Chem. Int. Ed. Engl., 1982, **21**, 810–819.
52. Demharter, A., Herdtweck, E., Hörl, W., Ugi, I. Herstellung chiraler 1,1'-Iminodicarbonsäure-Derivate aus α-Aminosäuren, Aldehyden, Isocyaniden und Alkoholen durch die diastereoselektive Fünfzentren-Vierkomponentenreaktion. – Angew. Chem., submitted 8 February 1995.
53. Ugi, I., Marquarding, D., Urban, R. Synthesis of peptides by four-component condensation – In: Weinstein, B. (ed.). Synthesis of Peptides by Four-Component Condensation. Marcel Dekker, New York, 1982, 245–289.
54. Ugi, I., Obrecht, R., Touré, S. Recent developments in ß-lactam synthesis by four component condensation. – Heterocycles, 1984, **21**, 271–277; Ugi, I. et al. New reactions and methods of the synthesis of ß-lactams. – In: ur Rahman, A., Le Quesne, P. W. (eds.). Natural Products Chemistry II, Springer, Berlin, 1988, 107–133; Ugi, I., Eckert, H. The role of isocyanides in the synthesis of ß-lactam antibiotics and related compounds. – In: ur Rahman, A. (ed.). Natural Product Chemistry, Vol. 12. Elsevier Science Publ., 1000A, Amsterdam, Netherlands, 1992, 113–143.
55. Joullié, M. M., Semple, J. E., Wang, P. C., Zenon, L. K. Total synthesis of (+)-furanomycine and stereoisomers. – J. Am. Chem. Soc., 1980, **102**, 7505–7510; Ruth, F. N., Joullié, M. M. The four component condensation. – Ibid., 1982, **104**, 5852–5853; Flanagan, D. M., Joullié, M. M. Observations on the stereochemical outcome of the Ugi four component condensation. – Synth. Comm., 1989, **19**, 1–12; Studies directed toward the total synthesis of 14-membered cyclopeptide alkaloids: Synthesis of a linear precursor to Numunularine-F linear. – Ibid., 1990, **20**, 459–467.
56. Bodanszky, M., Ondetti, M. A. Peptide Synthesis. Ed. Olah, G. A., J. Wiley & Sons, New York, 1966. I. Ugi thanks these authors for the very kind prognosis on p. 127 of the preparation of peptide derivatives by U-4CR. The peptide synthesis by stereoselective U-4CRs [53] was developed systematically for 35 years, and this desired method succeeded finally with Lehnhoff [62].
57. Kunz, H., Pfrengle, W. Asymmetric synthesis on carbohydrate templates: Stereoselective Ugi-synthesis of α-amino acid derivatives. – J. Am. Chem. Soc., 1988, **110**, 651–652; Carbohydrate as chiral templates: Asymmetric Ugi-synthesis of α-amino acids using galactoosyllamines as the chiral matrices. – Tetrahedron, 1988, **44**, 5487–5494.
58. Deffner, M., Deimer, K.-H., Jaeger, E., Stelzel, P., Thamm, P., Wendler, G., Wünsch, E. Synthese von Peptiden. Vol. XV/1, Part I; Vol XV/2, Part II. Eds. Müller, E., Wünsch, E. G. Thieme Verlag, Stuttgart, 1974.

59. Goebel, M., Ugi, I. *o*-Alkyl-D-glucoprianosylamines and their derivates. – Synthesis, 1991, 1095–1098.
60. Goebel, M. O-peralkylierte Glycopyranosylamine als chirale Auxiliare in Peptidsynthesen mittels stereoselektiver Vierkomponentenkondensationen. Doctoral Thesis, Chair I of Organic Chemistry, Technical University of Munich, D-85747 Garching, Germany, 1994.
61. Marquarding, D., Ugi, I. Unpublished experimental results at the Bayer AG at Leverkusen, Germany, 1965.
62. a) Lehnhoff, S. Die stereoselektive 4CC mit Glucosaminen als Peptidsynthese. Doctoral Thesis, Chair I of Organic Chemistry, Technical University of Munich, D-85747 Garching, Germany, 1994; b) Lehnhoff, S., Karl, R. M., Klösel, R., Goebel, M., Ugi, I. Stereoselektive Synthesen von Peptidderivaten mit 1-Amino-2-deoxy-2-acetamido-3,4,6-tri-O-acetyl-b-D-glucopyranose mittels Vierkomponentencondensation (U-4CR). – Angew. Chem., 1995, **107**, 10, 1208–1211. (Dedicated to the 80th birthday of Miklos Bodanszky.)
63. Lehnhoff, S., Ugi, I. Synthesis of 1,5-substituted tetrazoles from secondary thioamides. – Heterocycles, 1995, **40**, 2, 801–802.
64. Sheehan, J. C., Corey, E. – J. Org. React., 1957, **9**, 388–405.
65. a) Ugi, I., Steinbrückner, C. Über ein neues Kondensationsprinzip. – Angew. Chem., 1960, **72**, 267; Ugi, I., Steinbrückner, C. α-Addition von Immonium-Ionen und Carbonsäure-Anionen in Isonitrile. – Chem. Ber., 1961, **94**, 2802–2814; b) Ugi, I., Steinbrückner, C. Isonitrile II. Reaktion von Isonitrilen mit Carbonylverbindungen, Aminen und Stickstoffwasserstoffsäure. – Ibid., 1961, **94**, 734–742.
66. a) Dömling, A., Kehagia, K., Ugi, I. The formation of ß-lactam derivatives and a C3-symmetrical heterocycle from 5,6-dihydro-2H-1,3-oxazines. – Tetrahedron, 1995, **51**, 1, 139–144; b) Kehagia, K., Ugi, I. The synthesis of 4-acetoxy-azetidinones as key intermediates for ß-lactams. – Ibid., 1995, **51**, **53**, 9523–9530.
67. Neidlein, R. – Arch. Pharm. (Weinheim), 1965, **298**, 491–497; 1966, **299**, 603–608.
68. Ugi, I., Wischhöfer, E. Isonitrile XI. Synthese einfacher Penicillansäure-Derivate. – Chem. Ber., 1962, **95**, 136–140.
69. Sjöberg, K. Doctoral and Habil. Thesis. Technical University of Stockholm, 1970.
70. Schutz, A., Ugi, I., Kabbe, H. J. Synthesis of a penicillin derivative by a four-component condensation. – J. Chem. Res. (S), 1979, **157**, (M) 1979, 2064–2071.
71. Schutz, A., Ugi, I. Die Synthese eines Cephamderivats mittels Vierkomponentenkondensation. – Z. Naturforschung, 1979, **34b**, 1303–1306.
72. a) Demharter, A. Neue Varianten der diastereoselektiven Vierkomponentenkondensation. Doctoral Thesis, Technical University of Munich, D-85747 Garching, 1992; b) Demharter, A., Hörl, W., Ugi, I. Darstellung chiraler 1.1½-Iminodicarbonsäurederivate aus α-Aminosäuren, Aldehyden, Isocyaniden und Alkoholen durch diastereoselektive U-5CR. – Angew. Chem.; Angew. Chem. Int. Ed. Engl., submitted.
73. Gross, H., Gloede, J., Keitel, I., Dunath, D. α-Aminosäuren und Derivate. II. Isonitrilreaktionen mit Glyoxysäurederivaten. – J. Prakt. Chem., 1968, **4**; Reihe, **37**, 192–199.
74. Ugi, I., Offermann, K. Isonitrile XVIII. Hydantoin-Imide-(4). – Chem. Ber., 1964, **97**, 2276–2281.
75. Lehnhoff and Hanusch repeated in 1994 the old experiments of Offermann [74].
76. Gieren, A., Dederer, B., George, G., Marquarding, D., Ugi, I. Die Bildung von Aminomalonsäurederivaten als Nebenreaktion von Vierkomponentenkondensationen (4CC) und die röntgenographische Ermittlung der Struktur eines Vertreters. – Tetrahedron Letter, 1977, **18**, 1503.
77. Lohberger, S., Fontain, E., Ugi, I., Müller, G., Lachmann, J. Malonamide derivatives as by-products of four component condensation. The computer-assisted investigation of a reaction mechanism. – New J. Chem., 1991, **15**, 915–917.
78. Ugi, I., Fontain, E., Bauer, J. Transparent formal methods for reducing the combinatorial wealth of conceivable solutions to a chemical problem – computer-assisted elucidation of complex reaction mechanisms. – Anal. Chem. Acta, 1990, **235**, 155–161.
79. a) Bauer, J., Fontain, E., Ugi, I. IGOR and RAIN – the first mathematically based general purpose computer programs for the solution of constitutional problems in chemistry and

their use as generators of constitutional formulas. – Commun. Math. Chem., 1992, **27**, 31–47; Ugi, I., Bauer, J., Bley, K., Dengler, A., Dietz, A., Fontain, E., Gruber, B., Herges, R., Knauer, M., Reitsam, K., Stein, N. Computerunterstützte direkte Lösung chemischer Probleme – die Entstehungsgeschichte und gegenwärtiger Status einer neuen Disziplin der Chemie. – Angew. Chem., 1993, **105**, 2, 210–239; Angew. Chem. Int. Ed. Engl., 1993, **32**, 201–227; b) Ugi, I., Bauer, J., Blomberger, C., Brandt, J., Dietz, A., Fontain, E., Gruber, B., v. Scholley-Pfab, A., Senff, A., Stein, N. Models, concepts, theories, and formal languages in chemistry and their use as a basis for computer assistance in chemistry. – J. Chem. Inf. Comput. Sci., 1994, **34**, 3–16.

80. See also: Fischer, G. B., Juarez-Brambila, J. J., Garalski, C. T., Wipke, W. T. Novel conversion of aldehydes to boronic esters. Simultaneous IGOR2 computer generation and experimental observation of an unusual rearrangement of α-aminoboranes. – J. Am. Chem. Soc., 1993, **115**, 440–444.
81. Fontain, E. Kombinatorik und Metrik formaler Struktur- und Reaktionsgeneration. Habilitation Thesis, Technical University of Munich, 1995; an improved version of RAIN has been developed and will be sold soon by the Pharm-ECO Lab, R&D Production, 128 Spring Street, Lexington, MA 02173, USA.
82. Stein, N. New perspectives in computer-assisted formal synthesis design – treatment of delocalized electrons. – J. Chem. Inf. Comput. Sci., 1995, **35**, 305–309.
83. A similar computer program was developed on the basis of *xbe*- and *xr*-matrices in Ugi, I., Stein, N., Knauer, M., Gruber, B., Bley, K. New elements in the representation of the logical structure of chemistry by qualitative mathematical models and corresponding data structures. – Top. Curr. Chem., 1993, **166**, 199–233.
84. See also: Dugundji, J., Ugi, I. An algebraic model of constitutional chemistry as a basis for chemical computer programs. – Top. Curr. Chem., 1973, **39**, 19–64.
85. Ugi, I. In fond memory of James Dugundji's contribution in chemistry, who passed away in 1985. – In: Brandt, J., Ugi, I. (eds.). Computer Applications in Chemical Research and Education, 1985. A. Hüthig Verlag, Heidelberg, 1989, 345–366.
86. Dömling, A., Ugi, I. Die Siebenkomponentenreaktion. – Angew. Chem., 1993, **105**, 634–635; The seven-component reaction. – Angew. Chem. Int. Ed. Engl., 1993, **32**, 563–564.
87. Dömling, A. Doctoral Thesis, Technical University of Munich, D-85747 Garching, 1994.
88. C&EN, April 19, 1993, 32.
89. Bradley, D. New Scientist, July 3, 1993, 16.
90. Dömling, A., Ugi, I., Hertweck, E. Seven component reaction – scope and limitation. – Angew. Chem., submitted.
91. a) Ugi, I., Goebel, M., Gruber, B., Heilingbrunner, M., Heiß, C., Hörl, W., Kern, O., Starnecker, M., Dömling, A. Molecular libraries in liquid phase via Ugi-MCR. – Res. Chem. Intermed., 1995; Goebel, M., Ugi, I. Beyond peptide and nucleic acid combinatorial libraries – applying unions of multicomponent reactions towards the generation of carbohydrate combinatorial libraries. – Tetrahedron Letters, 1995, **34**, 6043–6046; b) Hough, R. A., Pinilla, C., Blondelle, S. E., Appel, J. R., Dooley, C. T., Cuervo, J. Generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery. – Nature (London), 1991, **354**, 84–87; Science, **266**, 2019–2022; Bio Techniques, 1992, **13**, 412–416; Jung, G., Beck-Sickinger, A. G. Methoden der multiplen Peptidsynthese und ihre Anwendungen. – Angew. Chem., 1992, **104**, 375–391; Multiple peptide synthesis methods and their applications. – Angew. Chem. Int. Ed. Engl., 1992, **31**, 367–383; c) Felder, E. R. – Chimia, 1994, **48**, 531–541; d) Pavia, M. R., Sawyer, T. K., Moos, W. H. – Bioorg. Med. Chem. Lett., **3**, 387–396; Liskamp, R. M. J. – Angew. Chem., 1994, **106**, 661–664; Opportunities for new chemical libraries: Unutural biopolymers and diversomers. – Angew. Chem. Int. Ed. Engl., 1993, **33**, 633–636; Chen, C., Ahlberg Randall, L. A., Miller, R. B., Daniel, A., Kurth, M. J. Analogous organic synthesis of small-compound libraries: Validation of combinatorial chemistry in small-molecule synthesis. – J. Am. Chem. Soc., 1994, **116**, 2661–2662; Kurth, M. J., Ahlberg Randall, L. A., Chen, C., Melander, C., Miller, R. B., McAlister, K., Reitz, G., Kang, R., Nakatsu, T., Green, C. – J. Org. Chem., 1994, **59**, 5862–5864; Gallop, M. A., Barrett, R. W., Dower, W. J., Fodor, S. P. A., Gordon, E. M. Applications of combinatorial

technologies for drug discovery. 1. Background and peptide combinatorial libraries. – J. Med. Chem., 1994, **37**, 1233–1248; Applications of combinatorial technologies to drug discovery. 2. Combinatorial organic synthesis, library screening strategies, and future directions. – Ibid., 1385–1389; Burgess, K., Kiaw, A. I., Wang, N. Combinatorial technologies involving reiterative division/coupling/recombination: Statistical considerations. – Ibid., 1994, **37**, 2985–2987; Mitchison, T. J. – Chem. & Biol., 1994, **1**, 3–6; Alpers, J. – Science, 1994, **264**, 1399–1401; Weber, L. Kombinatorische Chemie – Revolution in der Pharmaforschung. – Nach. Chem. Tech. Lab., 1994, **42**, 698–702; König, B. Kombinatorische Chemie. – Ibid., 1995, **42**, 149–158.

92. Still, W. C., Yoon, S. S. a) – Proc. Nat. Acad. Sci. USA, 1993, **90**, 10922–10926; b) Kurze Synthese eines neuartigen C3-symmetrischen Rezeptors für die sequenzselektive Bindung von Peptiden. – Angew. Chem., 1994, **106**, 2517–2520; Tetrahedron Letter, 1994, **35**, 6413–6416; Synthetic receptor binding elucidated with an encoded combinatorial library. – J. Am. Chem. Soc., 1994, **116**, 373–376, 7467–7468, 7955–7956; Sequence-selective peptide binding with a synthetic receptor. –Tetrahedron, 1995, **51**, 567–578.
93. DeWitt, S. H., Kiely, J. S., Stankovic, C. J., Schroeder, M. C., Cody, D. M. R., Pavia, M. R. Diversomers: An approach to nonpeptide, nonoligomeric chemical diversity. – Proc. Nat. Acad. Sci. USA, 1993, **90**, 6909–6913.
94. Carell, T., Wintner, E. A., Bashir-Hashemi, A., Rebek, J. Neuartiges Verfahren zur Herstellung von Bibliotheken kleiner organischer Moleküle. – Angew.Chem., 1994, **106**, 2159–2161; Angew. Chem. Int. Ed. Engl., 1993, **33**; Carell, T., Wintner, E. A., Rebek, J. Screeningverfahren in Lösung zur Isolierung biologisch aktiver Verbindungen aus einer Molekülbibliothek. – Angew. Chem., 1994, **106**, 2162–2164; Angew. Chem. Int. Ed. Engl., 1994; Carell, T., Wintner, E., Sutherland, A. J., Rebek, J., Dunayevskiy, Y. M., Vouros, P. New promise in combinatorial chemistry synthesis, characterization, and screening of small molecule libraries in solution. – Chemistry & Biology, 1995, **2**, 171–183; Smith, P. W., Lai, J. Y. Q., Whittington, A. R., Cox, B., Houston, J. G. Synthesis and biological evaluation of library containing potentially 1600 amides/esters. A strategy for rapid compound generation and screening. – Bioorg. Med. Letters, 1994, **4**, 2821.
95. Ugi, I., Dömling, A., Gruber, B., Heilingbrunner, M., Heiß, C., Hörl, W. Formale Unterstützung bei Multikomponentenreaktionen – Automatisierung der Synthesechemie. Conference poster, GDCh-Workshop, 16–18. 11. 1994 at Bitterfeld and in: Holl, R. (ed.). Software-Entwicklung in der Chemie. Gesellschaft Deutschen Chemiker, Frankfurt am Main, 1995, 113–128.
96. Armstrong, R. W. 'Combinatorial libraries related to natural products' at the ACS National Meeting in Anaheim, Calif. on April 2, 1995. – dto. Molecular diversity via a convertible isocyanide in the four component condensation. – J. Am.. Chem. Soc., 1995, **117**, 7842–7843.
97. Ugi, I., Rosendahl, F. K. Isonitrile XV. Δ^1-Cyclohexenyl-isocyanid. – Liebigs Ann. Chem., 1963, **666**, 65–67.
98. See ref. 92a. and Furka, A., Sebestyen, M., Dibo, G. – Int. J. Pept. Protein Res., 1991, **37**, 487–493; Bioorg. Med. Chem. Lett., 1993, **3**, 419–424; Lam, K. S. – Nature (London), 1991, **354**, 82–84; Zuckermann, R. N. – Ibid., 1992, **40**, 498–507.
99. Ugi, I., Dömling, A., Goebel, M., Hörl, W., Gruber, B., Heilingbrunner, M., Heiß, C. Conference Cambridge Healthtech Institute, 23–25 Jan. 1995.
100. Weber, L., Waltbaum, S., Broger, C., Gubernator, K. Optimisierung der biologischen Aktivität von Kombinatorischen Verbindungsbibliatheken durch einen genetischen Algorithmus. – Angew. Chem., 1995, **107**, 2452–2454; Optimization of the biological activity of combinatorial compound libraries by a genetic algorithm. – Angew. Chem. Int. Ed. Engl., 1995, **34**, 2280–2282.

MULTIKOMPONENTREAKTSIOONIDE JA NENDE PRODUKTIPANKADE PÕHJUSTATUD KIIRED JA KESTVAD MUUTUSED PREPARATIIVSES JA FARMATSEUTILISES KEEMIAS

Ivar UGI

Klassikalised keemilised sünteesid *n* lähteainest on $\geq(n-1)$ preparatiivse vaheastme jadad. Praegu võib niisuguste reaktsioonide produkte efektiivsemalt saada "ühepaja" U-4CR-i (4CR = 4-komponentne reaktsioon) abil, mis esmakordselt teostati 1959. aastal. Selles protsessis toimub amiinide, karbonüülühendite ja mitmete eri tüüpi hapete α-liitumine isotsüaniididekis. Järgnevad ümbergrupeerumised tekitavad suurema hulga produkte kui kõik klassikalised multikomponentreaktsioonid (inglise keeles MCR) kokku. Alates 1993. aastast on välja arendatud viie- ja rohkemakomponentsed MCR-id, mis on U-4(5)CR-i ja teiste 3(4)CR-ide ühendused.

Esimene U-4CR-i produktipank on esitatud raamatus "Isonitrile Chemistry", mis ilmus 1961. aastal. Viimaste aastate jooksul on MCR-ide produktipangad saanud väga populaarseks ning toonud kaasa olulise progressi preparatiivses keemias ja farmatseutilises uurimistöös. Vedelik-MCR-ide produktipankades sisalduvaid bioloogiliselt aktiivseid keemilisi ühendeid saab eriti kergesti leida arvutikeemia uute algebraliste meetodite abil.

БЫСТРЫЕ И ПЕРМАНЕНТНЫЕ ИЗМЕНЕНИЯ В ПРЕПАРАТИВНОЙ И ФАРМАЦЕВТИЧЕСКОЙ ХИМИИ, ВЫЗВАННЫЕ МУЛЬТИКОМПОНЕНТНЫМИ РЕАКЦИЯМИ И ИХ БИБЛИОТЕКАМИ

Ивар УГИ

Классические схемы органического синтеза, начинающиеся с *n* числа ингредиентов, включают $\geq(n-1)$ химических стадий. Однако синтез целевых продуктов можно осуществить и более эффективно через мультикомпонентные реакции "одного горшка" U-4CR. При этом амины, карбонильные соединения и различные типы кислот подвергаются в присутствии изоцианидов α-присоединениям и последующим перегруппировкам. Это обеспечивает большее разнообразие получаемых веществ, чем все классические MCR, вместе взятые. Начиная с 1993 г. созданы более чем 5-компонентные MCR, сочетающие U-4(5)CR с другими 3(4)CR.

В 1961 г. автор создал первую библиотеку U-4CR и опубликовал ее в своей монографии "Isonitrite Chemistry". В последние годы библиотеки MCR завоевали большую популярность, так как привели к прогрессу в синтетической химии и фармацевтических исследованиях. Так, биологически активные вещества библиотек MCR могут быть легко найдены с помощью созданных компьютерных алгебраических программ.