Since 1995 the New Chemistry of Multicomponent Reactions and Their Libraries, Including Their Heterocyclic Chemistry

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Dedicated to Wolf-Peter Fehlhammer

A growing number of products, including many heterocycles, can be prepared by the one-pot MultiComponent Reactions (MCRs) just by mixing three or more educts, and in many cases practically quantitative yields of pure products can be obtained. The 3CR by α-aminoalkylations of nucleophiles began in the middle of the last century, and the syntheses of heterocycles by MCRs of three and four components were introduced by Hantzsch in the 1880s. The MCRs of the isocyanides with four and more educts began in 1959, and their compound libraries were mentioned since 1961. However, only since 1995 the often automated one-pot chemistry of the MCR of the isocyanides is used extensively. If a chemical compound can be prepared by a sequence of two component reactions or a suitable MCR, the latter is always a superior procedure. The U-4CR can be combined with other chemical reactions and MCRs as one-pot reactions of $n > 4$ components, and such unions even have a much greater variety of structurally and stereochemically different products. The educts and products of Ugi-type MCRs are more variable than those of all previous chemical reactions and other MCRs. Due to the progress in screening and automation processes in the last few years, many new compounds have been formed and investigated more rapidly than ever before. The search for new desirable products can be accomplished more than 10,000 times faster than by the older conventional methods. The now popular chemistry of the MCRs of the isocyanides fills the since long empty part of organic chemistry.

J. Heterocyclic Chem., **37**, 647 (2000).

Introduction.

The previously moderately used chemistry of MCRs, and particularly their libraries that are often automatically accomplished, have suddenly become one of the favoured research methods of the chemical industry since 1995.

In principle all chemical reactions correspond to equilibria between one or two educts and products, but the preferred preparative chemical steps correspond to practically irreversible reactions. Without competing formations of by-products, quantitative yields of products can be obtained. The usual syntheses of chemical compounds from three or more ($N \geq 3$) different starting materials correspond to sequences of preparative steps (M) that increase with the number of educts ($M \geq N - 1$). After each step its intermediate or final product must be isolated and purified. With each preparative step the amount of work increases, and the yield of the product decreases.

Alternatively a great variety of chemical compounds can also be formed directly from three and more different educts by one-pot multicomponent reactions (MCRs), and under optimized reaction conditions quantitative yields of products can be obtained [1-7]. Whenever a product is formed by a suitable MCR, this has obvious advantages over any multistep procedures.

Three basic types of MCRs are known. Type I corresponds to a collection of equilibrating subreactions between educts, intermediate and final products. Type II has equilibrating reactions between the educts and intermediate products, but their final formations of products proceed irreversibly. The MCRs of type III are sequences of irreversible subreactions that proceed towards their product [4].

The first MCR was accomplished by Laurent and Gerhardt [8] in 1838. They mixed bitter almond oil and ammonia, and from that a product "benzoylazotid" resulted from ammonia, hydrogen cyanide and two parts of benzaldehyde [9]. In 1850 Strecker [10] began to convert carbonyl compounds, hydrogen cyanide and ammonia into the derivatives of aminomethyl cyanides. Then, after the First World War the Mannich reaction [11] was introduced. In 1960 Hellmann and Opitz described in their book of α-Aminoalkylierung [9] that most of the classical reactions of three components (3CRs) are α-aminoalkylations of nucleophiles, the so-called HO-3CRs, of type I which equilibrate, and usually therefore low yields of products result. Many advantageous syntheses of heterocycles that usually belong to type II reactions consist of MCRs of bi-functional educts and begin with α-aminoalkylations to react further, forming irreversibly their final products. Preparative reactions of type III are rare [12], but in the biochemistry of living cells the majority of compounds are formed by processes of type III.

Essential Steps of the Isocyanide Chemistry.

The chemistry of the isocyanides began in 1859, but for a whole century its subsequent activities remained moderate [13]. This was mainly due to two reasons: At that time

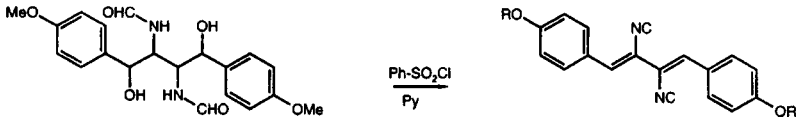
the isocyanides could not yet be prepared sufficiently well, and then the known ones had intensely unpleasant smells [13]. One of the activity islands was the introduction and investigation by Passerini's reaction [13-15] in the decade of 1921-1931. This P-3CR was the first MCR of the isocyanides of type II, where carbonyl compounds, carboxylic acids and isocyanides form α-acyloxycarboxamides.

In 1948 Rothe [16] discovered the natural product *Xanthocilline* **2a** containing a diisocyanide moiety, which was later used as an antibiotic. In 1956 Hagedorn and Tönje [17] formed the *O,O'*-dimethylderivative **2b** by the first dehydration of an *N*-formylamine **1**.

The isocyanides **5** are the only organic compounds that contain a functional group with a divalent carbon atom C^{II}, and almost all of their reactions are exothermic α-additions of α-aminoalkyl cations and anions onto the C^{II} of the isocyanides, whose carbon atom becomes then a C^{IV}. Often these α-adducts undergo rearrangements to their final products, whose constitutional structure depends on the last reaction [13].

As soon as the isocyanides became well available, the four component reaction of the isocyanides was introduced [23,24]. Since 1962 it is mentioned as the Ugi-reaction [15a,25], which is abbreviated as the U-4CC [1] or the U-4CR [2]. The U-4CR can formally be considered as a union [26] of the HO-3CR and the P-3CR.

Scheme 1

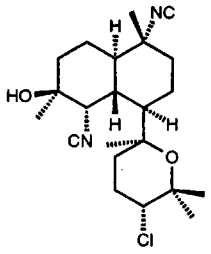


1 **2** **2a**: R = H, **2b**: R = Me

Later many naturally occurring isocyanides were found, and several of them have interesting plant protecting or pharmaceutical properties [6,7]. Recently Miyaoka *et al.* [18] discovered in the Okinavian marine sponge three diisocyano diterpenoids. Its product *Kalihinol A* **3** has *in vitro* an unusually efficient antimalarial activity.

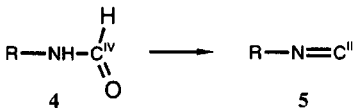
The educts and products of the U-4CR are more variable than those of any previously introduced chemical reaction, not only since this reaction uses four functional groups of the educts. In 1993 it was realized that even higher numbers of educts can participate, if the U-4CR can be combined with other reactions, also including further MCRs and their unions [26], which increase their variability very much [4,7].

Scheme 2



3
Kalihinol A

Scheme 3



4 **5**

Early Preparative Progress in the Isocyanide Chemistry.

A new era of isocyanide chemistry began in 1958, when the isocyanides **5** became generally well available by the dehydration of the *N*-formylamines **4** [19]. The alkylformylamines are easily converted into their isocyanides by phosgene, or its dimer [20], or its trimer [21] in the presence of suitable amines like trialkylamines or pyridine [13]. Since 1985 the alkyl- and arylisocyanides can usually be well formed by the combination of phosphorous oxychloride ($POCl_3$) and diisopropylamine [22].

In 1961 it was mentioned that the U-4CR of four collections of different educts can form large collections of products as libraries. In 1982 Furka [27,28] began to produce and to investigate the solid-phase multistep libraries of peptides, and since then the formation of various types of libraries were produced and investigated. Since 1995 the one-pot libraries of the U-4CRs and their unions with other reactions are used with still increasing activities, particularly in the industry [7].

The U-4CR.

Particularly in the chemical industry, the U-4CR is nowadays used very often, since their products can be prepared by minimal preparative work, and usually in very high yields and are thus easy to automate. In 1961 it was demonstrated that educts of a U-4CR can simultaneously form 10,000 substitutionally different products if all four classes of educts contain 10 different starting materials [29]. In the search for new products libraries of the U-4CR and related processes are now formed and industrially investigated very intensely [4,6,7].

The U-4CRs form their products from amines, aldehydes or ketones, acids and isocyanides. In contrast to other reactions, the U-4CR can form a very great variety of constitutionally different types of products, whose different types of acid and amino components determine their structural features. If a U-4CR proceeds too slowly, then instead of the amine and carbonyl components, their Schiff bases or enamines are reacted with the acid and isocyanide. Under suitable reaction conditions their products are then very quickly formed, and their yields are often almost quantitative [7]. In contrast to most other chemical reactions, the U-4CR and related processes allow all combinations of their educts to form their products. These reactions proceed though their educts form products that are extremely crowded. Thus, it was recently demonstrated that even the tripeptide **9** can be formed by a U-4CR, which cannot be produced by any other reaction [30].

The *Xylocain*™ **14** of the AB Astra in Sweden was one of the most popular local anaesthetics, which was originally prepared by several different multistep procedures [31]. In January 1959 Ugi and co-workers [23] introduced a new way of producing **14** by the U-4CR. The *Xylocain*™ **14** was then the only widely used product of its type, but in the last few years more than 20 different but closely related products were derived. All of these compounds could be formed in one step by a U-4CR [7].

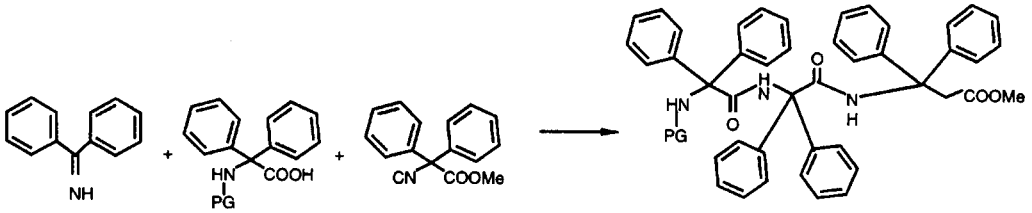
The products shown in Scheme 6 were directly formed by the U-4CR. They were thus always easier and in higher yields prepared than by any different way that consisted of some multistep syntheses [4,7].

Generally there are two ways of the formation of heterocyclic compounds by MCRs. Either the heterocycle is formed during the MCR - quasi de novo - or the heterocycle is part of a starting material and is diversified during the MCR.

Is the heterocyle synthesized during the MCR? One can distiguish between the heterocycle formation as an intrinsic consequence of a starting material (inner circle of Scheme 7) or as a consequence of a combination of functional groups of one or more classes of starting materials (outer circle of Scheme 7).

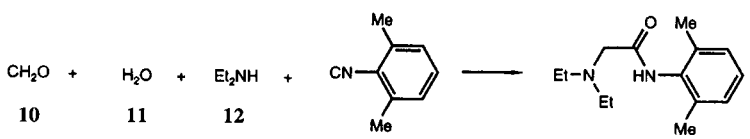
Recently the Merck Research Laboratory prepared the HIV protease inhibitor *Crixivan*™ (MK 639) **20** by a U-4CR as the central step. Thus, the number of preparative steps towards **20** could be tremendously reduced [32].

Scheme 4



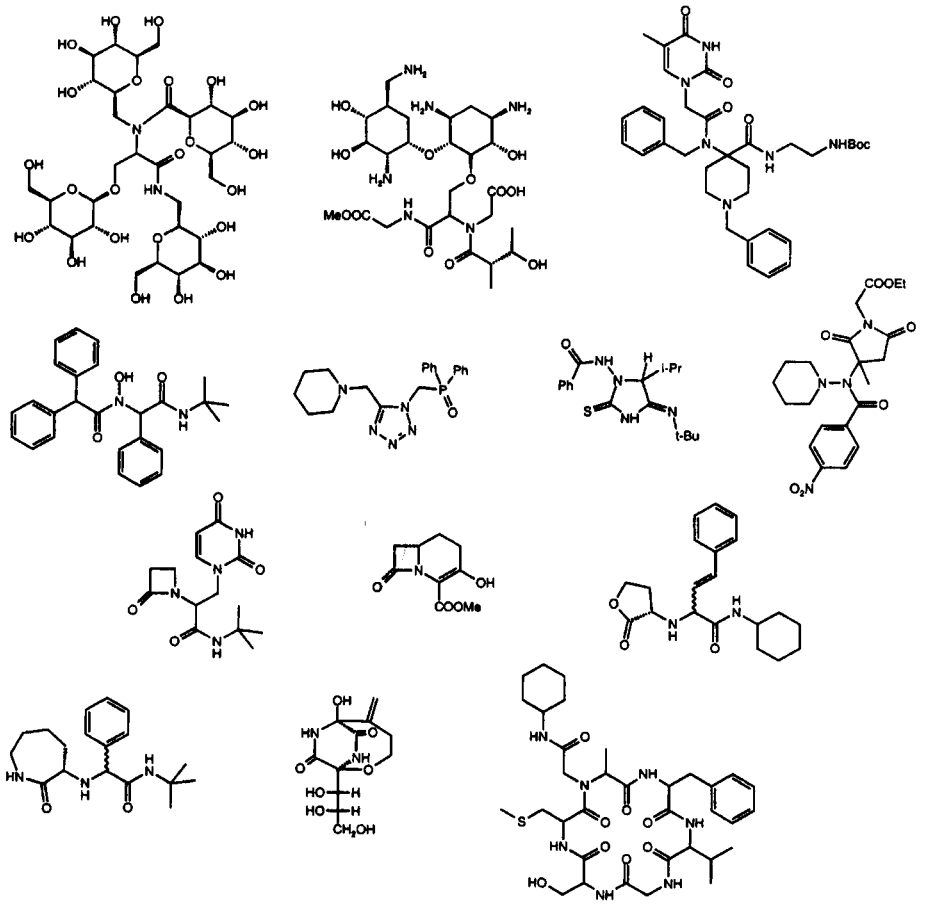
6 7 8 9

Scheme 5

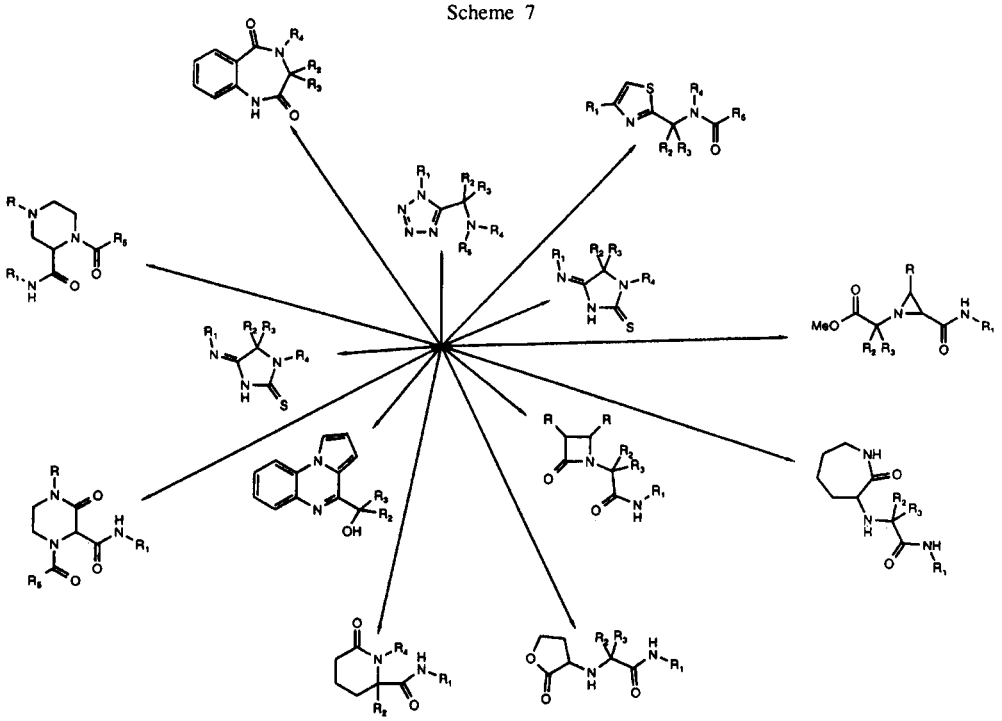


10 11 12 13 14

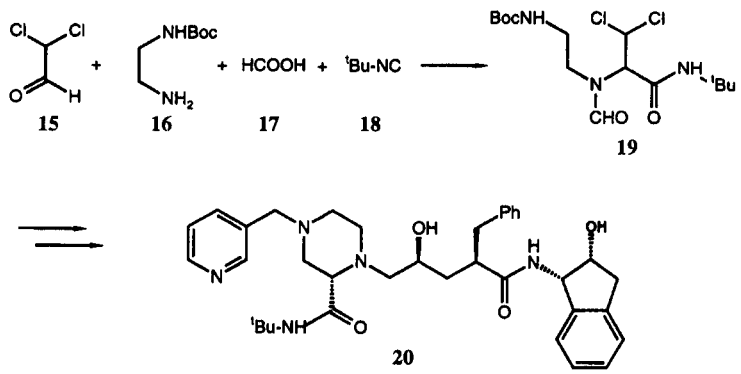
Scheme 6



Scheme 7



Scheme 8



Crixivan (MK 639)

Stereoselective U-4CR and the Preparation of α-Amino Acid Derivatives.

The stereoselective U-4CRs are most often accomplished by using chiral primary amines. Under suitable conditions one of the stereoisomeric products is preferentially formed. However, in many cases the other stereoisomer can also be formed by a U-4CR, if the reaction conditions are changed [33,34].

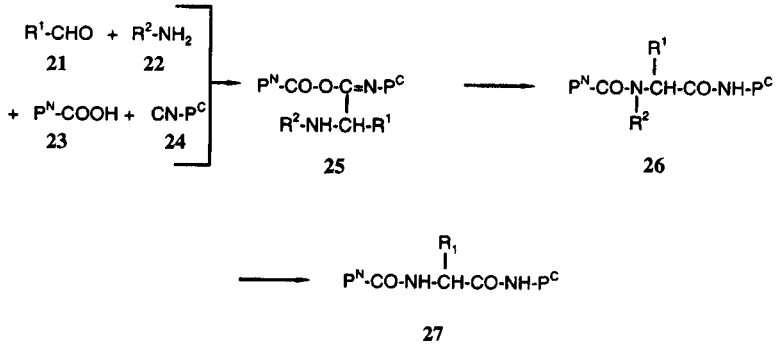
It was recognized very early that one of the most interesting areas of the stereoselective U-4CR chemistry is the direct formation of derivatives of α-amino acids and peptides [13,35], but it was only gradually realized that such one-pot syntheses cannot be easily accomplished. A suitable program of sufficient research was carried out; this required almost four decades of investigations. Scheme 9 shows the formation of new peptide bonds by reacting N-protected α-amino acid or peptide derivatives **23** with carbonyl compounds **21**, amines **22** and isocyano components with a protected carboxyl group **24**.

Since 1961 it was tried to find ways of preparing derivatives of α-amino acids and peptides by stereoselective U-4CRs. It was quickly realized that the best way of preparing chiral α-amino acid derivatives by stereoselective U-4CRs is to use chiral primary amine components with an alkyl group, whose *N*-alkyl group can be replaced by a proton [24,34b].

After a systematic pre-study [36], it was recognized that the course of the stereoselective U-4CR depends particularly much on its reaction conditions. The reaction mechanism of a U-4CR was investigated. The experimental results were evaluated by mathematical and computer oriented methods which led to a general understanding and an improved planning of further investigations and formations of products, including the chiral ones [13,37].

Since 1969 several methods of preparing chiral α-ferrocenyl alkylamines were introduced, which are nowadays an essential method of preparing new stereoselective catalysts [38]. Before that, α-ferrocenylamines were used as components of the U-4CR, since suitable compounds of

Scheme 9



this type have the unique advantage that they can be converted into α-amino acid derivatives whose *N*-α-ferrocenyl group can be replaced by a proton in that way that the chiral α-ferrocenyl alkylamine is simultaneously resynthesized [34b]. However, in principle this ideal process had the disadvantage that the yield and stereoselectivity of the U-4CR does not proceed sufficiently well, and some other steps have further disadvantages [39].

In 1988 Kunz *et al.* [40] introduced the U-4CR with the 2,3,4,6-tetra-*O*-pivaloyl-ß-D-galactopyranosylamine **28** or related sugar-based chiral amine components. It seems that such reactions are limited to formic acid as the acid component, forming thus very stereoselectively chiral α-amino acid derivatives in excellent yields. However, its stereoselectivity-inducing assisting group can be removed only by hydrolyses with hot hydrochloric acid to obtain α-amino acids.

Since this group did not continue, several years later Ugi *et al.* [41] began to investigate the use of many different aminocarbohydrates, in order to find related amine components that react at least equally well, so that peptide derivatives whose products should be cleavable under sufficiently mild conditions can generally be prepared by U-4CRs.

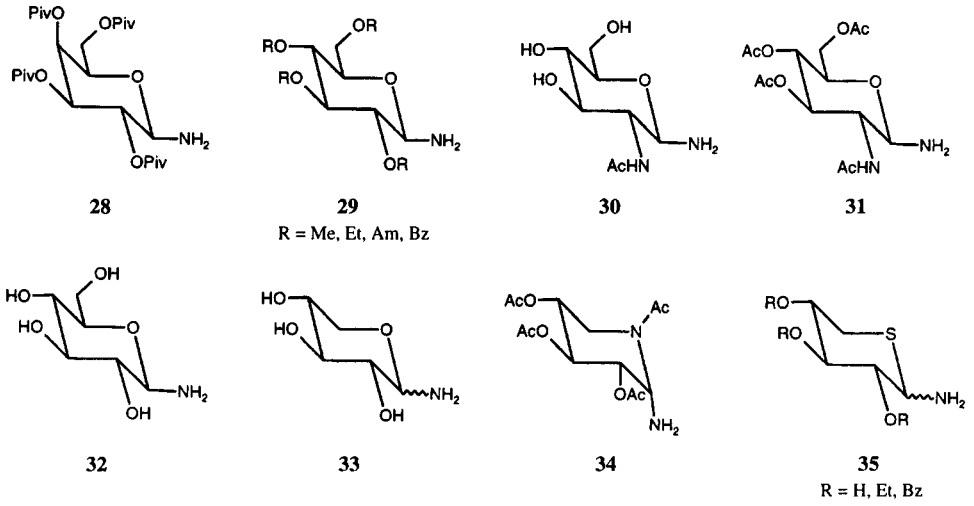
steps in relatively good yield, and this amine component can be converted stereospecifically into the U-4CR products, whose xylose derivatives can be replaced by a proton under extremely mild conditions [43]. This almost ideal reacting 1-amino-5-acetamino component of U-4CRs has the disadvantage, that its synthesis requires too much work.

The 1-amino-2-acetylaminoglucose **30** can be formed easily from the easily available 2-acetylaminoglucose and ammonium carbonate [44]. The peptide derivatives that result from the U-4CRs with this amine can be cleaved easily under selected conditions by methanolic HCl [45]. It is now realized that glucose and xylose react also with ammonium carbonate to form their corresponding 1-amino derivatives **32** and **33** [45], and also the 5-mercapto-5-deoxyxyloses can thus be converted into their 1-amino compounds **35** [46].

The Modern Unions of the U-4CR with Other Reactions.

Shortly after the introduction of the U-4CR some ß-amino acids were converted into ß-lactams [47b] and at that time methanol and CO_2, which equilibrate with methoxycarboxylic acid, were used as acid component of the U-4CR [47a]. Only in the last few years it was realized that such reactions belong to general concepts: educts with many

Scheme 10



At first *O*-alkylaminosaccharides like **29** were investigated. They react in U-4CRs to *N*-protected α-amino acid and peptide derivatives which can be cleaved under somewhat milder conditions, but not yet sufficiently well. The U-4CRs with the subsequently introduced 1-amino-2-acetylamino-*O*-acylglucose derivatives **31** proceeded very well, but their products were not yet cleaved as sufficiently well, as desired [42].

The 1-amino-5-acetamino-5-deoxy-2,3,4-tri-*O*-acetyl-α-D-xylopiperidinose **34** can be formed by 12 preparative

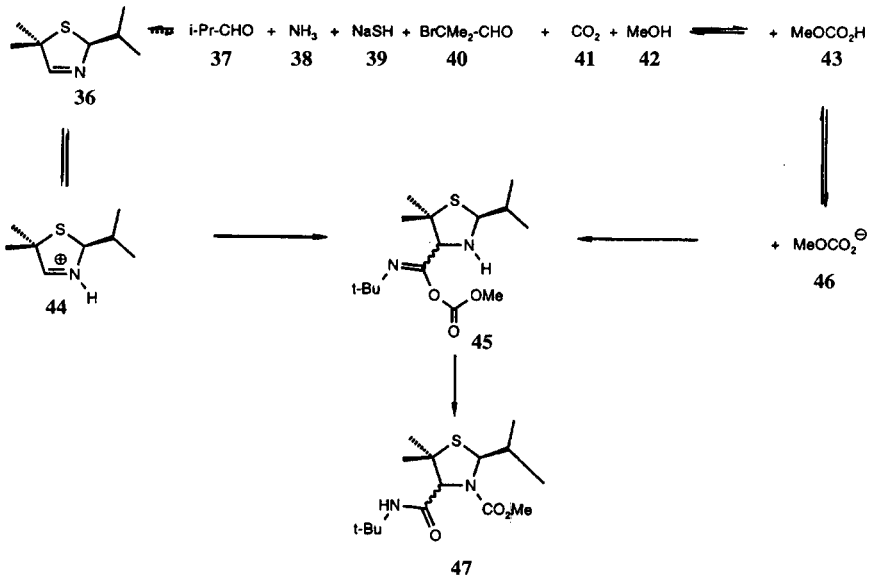
suitable functional groups can undergo MCRs, and the U-4CR can be combined with other reactions as their union [1].

In 1993 a union of two other reactions, an equilibrating reaction of methanol and CO_2 and the educts of an MCR of Asinger were combined with a U-4CR, so that ultimately MCRs of six or seven components could form their products like **47** [48], and shortly thereafter the general scheme of such and related reactions was described [49]. Gruber *et al.* represented the generalized, mathematically

oriented chemistry at the German chemical conference at Bitterfeld [50]. Shortly thereafter Dömling and Gruber presented three posters about such MCRs and their libraries at a conference about pharmaceutically oriented chemistry at La Jolla [51].

Besides the usual U-4CRs, those of multifunctional educts and their unions with other chemical processes are now increasingly accomplished, because further structurally different types of products can be obtained, which is illustrated here by a few examples.

Scheme 11



It seems that these events stimulated many chemists, since in 1995 the MCRs of the isocyanides and their libraries became increasingly active, when Armstrong published his syntheses of natural products and related products by the U-4CR and their libraries. At the Hofmann LaRoche company, Weber *et al.* [52] combined the chemistry of the U-4CR libraries with mathematically oriented methods and described the formation of new compounds by U-4CRs and their libraries. With these methods they quickly found new antithrombine compounds [52a]. Shortly thereafter industrial chemistry began the search for new products by MCRs and their libraries were obtained more intensely than by other comparable methods [27,53].

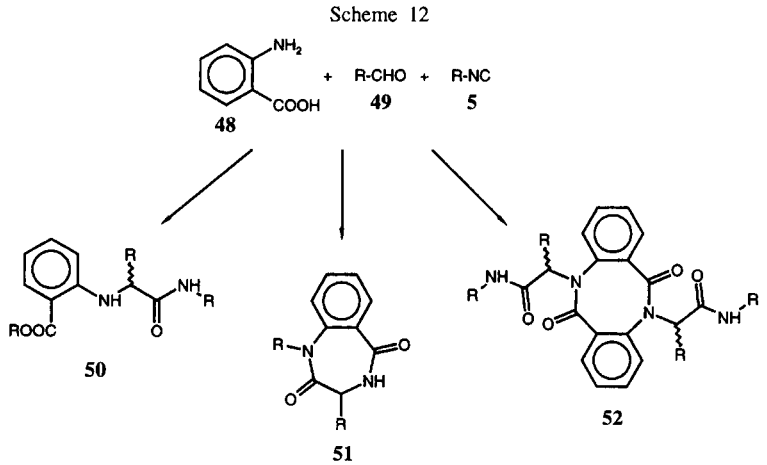
Formation of Products by MCRs of the U-4CRs with Multifunctional Educts and Their Unions with Other Reactions.

2-Aminobenzoic acid **48** can react with aldehydes and isocyanides to form their different products directly or with further reagents, depending on reaction conditions, as is illustrated in Scheme 12 [54].

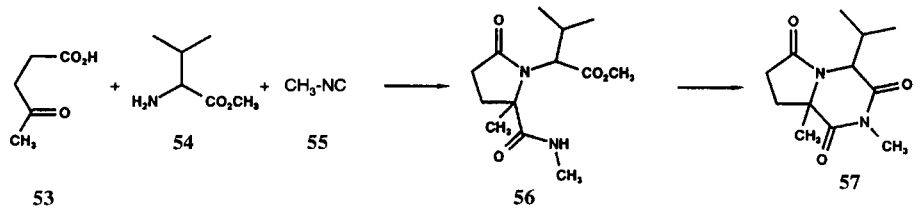
Usually products of the type **50** are formed extremely well, and under somewhat different conditions also compounds like **51** and **52** can result.

The heterocycles **56** and **57** can analogously be formed from γ-carbonylic acids **53**, amino acid esters **54** and isocyanides **55** [55].

Scheme 12



Scheme 13

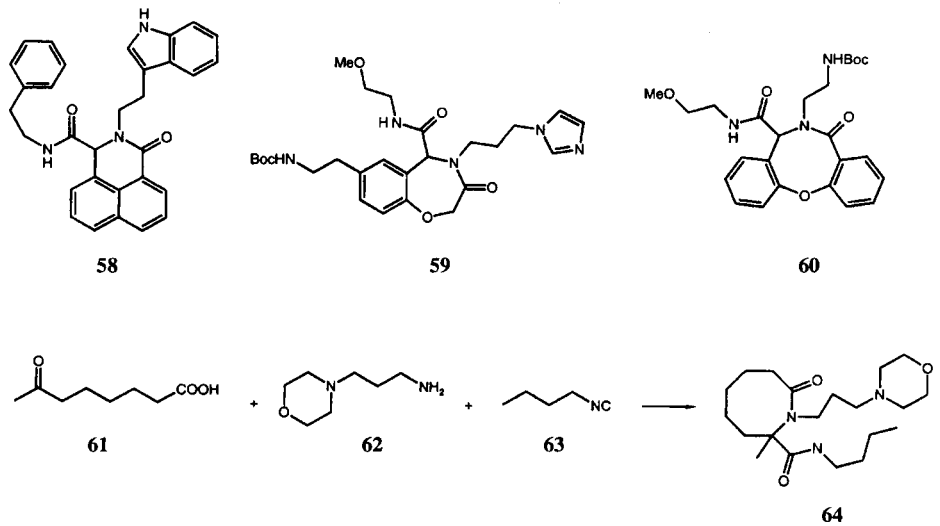


53 54 55 56 57

Schemes 14-19 illustrate in how many different ways heterocyclic products can be made by the U-4CR and subsequent reactions.

Short *et al.* published the formation of products **64**. Analogously the heterocyclic compounds **58**, **59** and **60** were synthesized [56].

Scheme 14

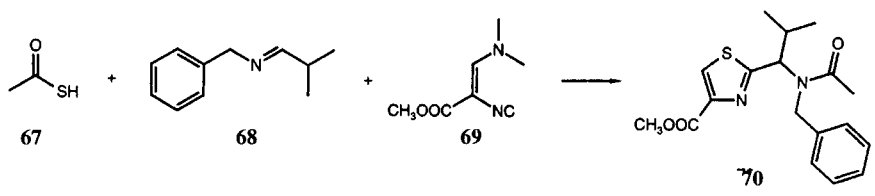


58 59 60

61 62 63 64

A variety of products could be formed by U-4CR related reactions of carboxylic acids, whose functional groups have distances of five to seven atoms [57].

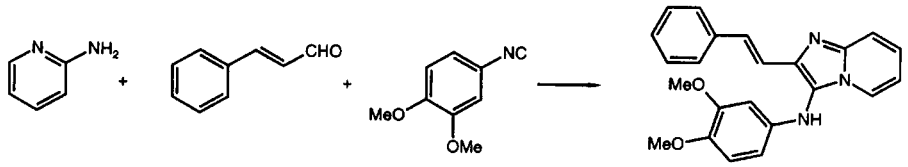
Scheme 15



67 68 69 70

Scheme 16 illustrates an example where the pyridine **71** reacts as acid component [58].

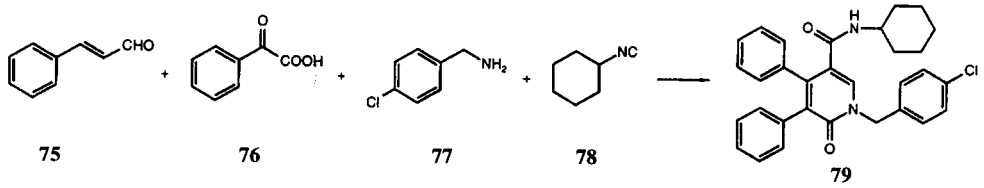
Scheme 16



71 **72** **73** **74**

The pyridone **79** is formed by a U-CR followed by ring closure after base treatment [59].

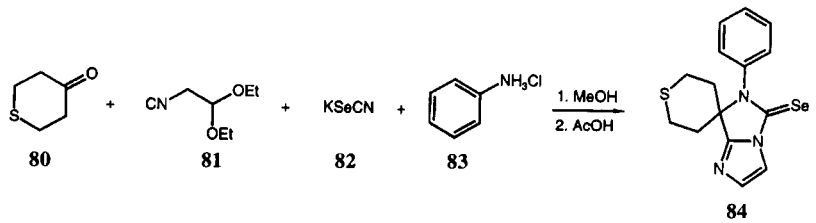
Scheme 17



75 **76** **77** **78** **79**

In 1993 Bossio *et al.* presented the synthesis of compound **84**, whose formation also consists of a U-4CR and subsequent ring closure [60].

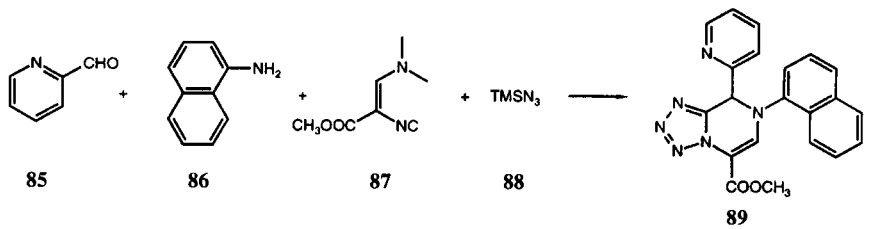
Scheme 18



80 **81** **82** **83** **84**

Another example of the great variability of the Ugi reaction is the formation of the bicyclic tetrazole derivative **89** shown in Scheme 19 [61].

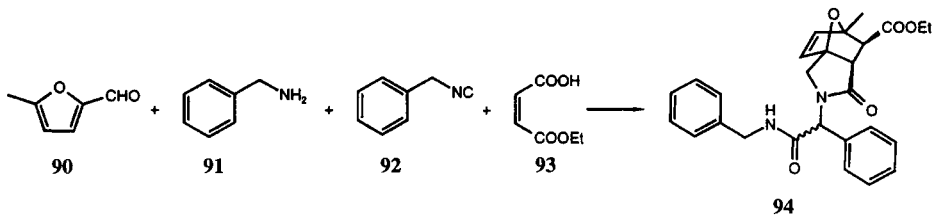
Scheme 19



85 **86** **87** **88** **89**

A combination of a cycloaddition and a U-4CR is described by Scheme 20 [62].

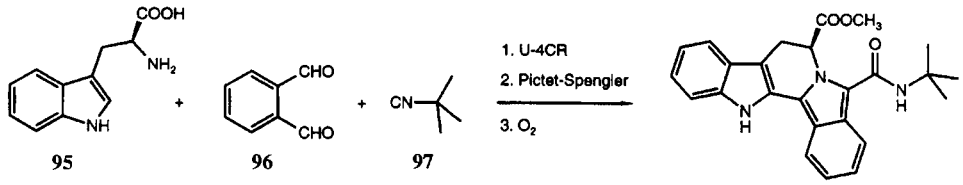
Scheme 20



90 91 92 93 94

The one-pot combination of several reactions is illustrated by Scheme 21 [63].

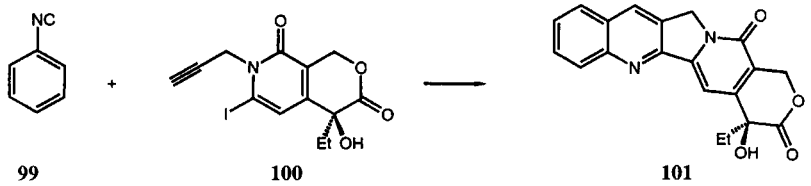
Scheme 21



95 96 97 98

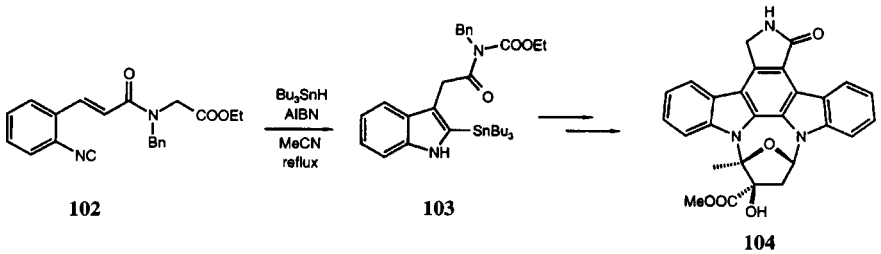
The elegant syntheses of the natural products **101** (Scheme 22) [64] and **104** (Scheme 23) [65] by Currant *et al.* illustrate heterocycles forming reactions of the isocyanides that are MCRs, which are related to the U-4CR but differ from them essentially.

Scheme 22



99 100 101

Scheme 23



102 103 104

In recent years more new chemical compounds have been formed by MCRs than a few years earlier, and the chemistry of the isocyanides is increasingly being used.

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