PART 1

GREEN REAGENTS

1

THE FOUR-COMPONENT REACTION AND OTHER MULTICOMPONENT REACTIONS OF THE ISOCYANIDES

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INTRODUCTION

The usual syntheses of products from three or more educts require several preparative processes, and its intermediate or final product must be isolated and purified after each reaction. As the number of steps increase, the amounts of solvents and the preparative work grows, while the yields of products decrease and more and more solvents and by-products must be removed. In such reactions, scarcely all optimal aspects of green chemistry can be accomplished simultaneously.

Practically irreversible multicomponent reactions (MCRs), like the Ugi 4-component reaction (U-4CR), can usually fulfill all essential aspects of green chemistry. Their products can be formed directly, requiring minimal work by just mixing three to nine educts. Often minimal amounts of solvents are needed, and almost quantitative yields of pure products are frequently formed.

The chemistry of the isocyanide U-4CR was introduced in the late 1950s, but this reaction was relatively little used for more than three decades, only around 1995 almost suddenly it was recovered by the chemical industry.[1]

In the last few years the variability of educts and products of the U-4CR has essentially increased, so that by now the majority of new products have been prepared. The U-4CR allows the preparation of more different types of products than

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any other reaction. If such a product with desirable properties—a lead structure—is found, large amounts of related compounds can be prepared easily by the U-4CR and similar reactions.

It is barely possible to still find novel reactions of one or two components, whereas the chemistry of the MCRs is not yet exhausted. Still, many new combination of up to nine different types of MCR educts can form new types of products that can totally differ from the already known chemistry.[1]

1.1 THE CLASSICAL MCRs

Chemical reactions are in principle equilibria between one or two educts and products. In practice, the preferred preparative reactions proceed irreversibly. Syntheses of products from three or more educts are usually sequences of preparative steps, where after each reaction step its intermediate or final product must be isolated and purified while the yield decreases. Exceptions can be the reactions of three components on solid surfaces and also some MCRs with α-additions of intermediate cations and anions onto the isocyanides.[1,2]

Besides the usual chemistry, an increasing number of chemical compounds can be prepared by MCRs just by mixing more than two educts.[3–5] Such processes do not proceed simultaneously, but they correspond to collections of subreactions, whose final steps form the products. Any product that can be prepared by an MCR whose last step is practically irreversible requires considerably less work and is obtained in a much higher yield than by any conventional multistep synthesis.

Three basic types of MCRs are now known.[5] The MCRs of type I are collections of equilibrating subreactions. In type II the educts and intermediate products equilibrate, but their final products are irreversibly formed. The MCRs of type III correspond to sequences of practically irreversible reactions that proceed from the educts to the product.[6]

In 1960 Hellmann and Opitz[7] introduced their α-*Aminoalkylierung* book, wherein they mentioned that the majority of the "name reactions" by MCRs belong together since they have in common their essential features. This collection of 3CRs can be considered as Hellmann–Opitz 3-component reactions, (HO-3CRs). They are either α-aminoalkylations of nucleophiles of MCR type I, or they form intermediate products that react with further bifunctional educts into heterocycles by 4CRs of type II. Their last step is always a ring closure that proceeds irreversibly.

This MCR chemistry began in 1850 when the Strecker reaction S-3CR[8] of ammonia, aldehydes, and hydrogen cyanide was introduced. Since 1912 the Mannich reaction M-3CR[9] of secondary amines, formaldehyde, and β-protonated ketones is used.

The MCRs of type II forming heterocycles begin with α-aminoalkylations of nucleophilic compounds, and subsequently these products react further with bifunctional educts whose last step is always an irreversible ring formation. Such

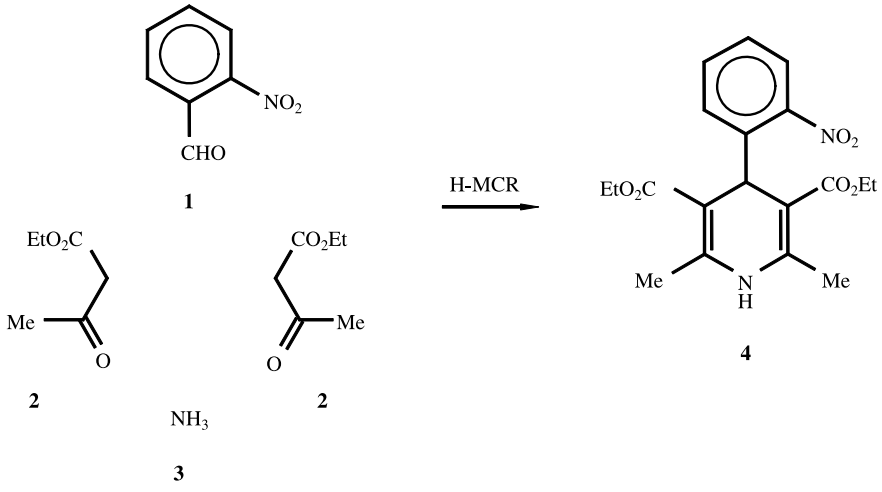
reactions were introduced in 1882 by Hantzsch[10] and by Radziszewski.[11] Shortly after this Biginelli[12] also entered a similar type of forming heterocycle by MCRs. In the 1920s Bucherer and Bergs[13] began to produce hydantoin derivatives by BB-4CRs. This reaction begins with an S-3CR whose product then reacts with CO_2 and forms irreversibly the hydantoin. The products of the S-3CR and of the BB-4CR can both be hydrolized into α-aminoacids, but the synthesis via the BB-4CR is used preferentially, since this leads to products of higher purity and with higher yields.

In the early Gatterman's preparative chemistry book,[14] the one-pot synthesis of dihydropyridine derivatives like those formed by the Hantzsch reaction was one of practical laboratory exercises.

Schildberg and Fleckenstein observed that calciumantagonists can advantageously influence the peripheric vessels and those of the heart.[15] With the 4-aryldihydropyridine-3,5-dicarboxylic esters **4** (Scheme 1.1) that have such effects, the first pharmaceutical products synthesized by Hantzsch reactions were independently introduced by the Bayer AG[16] and Smith Cline & French.[17]

As the last classical MCR in the 1950s, Asinger[18] introduced the 3CRs and 4CRs to form thiazole derivatives. It seems that these A-MCRs can belong to type I or to type II.

In preparative chemistry only a few MCRs of type III are known;[6] however, in living cells, the collections of the biochemical compounds are formed by MCRs of type III. In that case the formation of the individual products proceeds by subreactions that are accelerated by the enzymes present in the suitable areas within the living cells. The resulting collections of products can be considered to be their libraries.



Scheme 1.1 Hantzsch synthesis of 4-aryldihydropyridine-3,5-dicarboxylic esters.

1.2 THE FIRST CENTURY OF THE ISOCYANIDES

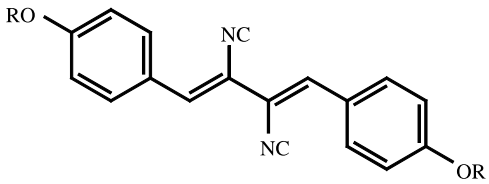
The chemistry of the isocyanides[3] began when, in 1859 Lieke[19] formed allyl isocyanide from allyl iodide and silver cyanide, and when, in 1866 Meyer[20] produced in the same way 1-isocyano-1-desoxy-glucose. In 1867, Gautier[21a] used this procedure to prepare alkylisocyanides, and Hofmann[22] introduced the formation of isocyanides from primary amines, chloroform, and potassium hydroxyde. Gautier[3,21b] also tried to prepare an isocyanide by dehydrating an amine formiate via its formylamine using phosphorus pentoxide, but this process produced no isocyanide. Gautier had not yet realized that acidic media destroyed the isocyanides.

However, for a whole century the chemistry of the isocyanides remained as a rather empty part of organic chemistry, since they were not yet easily available, and furthermore they had a very unpleasant smell. At that time, only 12 isocyanides had been prepared and only a few of their reactions had been investigated.[3]

In the 1890s, Nef[23] mentioned that the functional group —NC of the isocyanides contains a divalent carbon atom C^{II}, and therefore there is a large difference between their chemistry and that of the other chemical compounds that contain only tetravalent carbon atoms C^{IV}. Any synthesis of isocyanides corresponds to a conversion of C^{IV} into C^{II}, and all chemical reactions of isocyanides correspond to transitions of the carbon atoms C^{II} into C^{IV}.

In this period, the most important reactions of the isocyanides were the formations of tetrazole derivatives from isocyanides and hydrazoic acid, a process introduced in 1910 by Oliveri-Mandala and Alagna,[24] and then in 1921 Passerini introduced the reaction (P-3CR),[25] which was the first 3-component reaction of the isocyanides. In the 1940s Baker,[26] and later Dewar,[27] proposed mechanisms of the P-3CR. The important role of the intermediate hydrogen bond between the carboxylic acid and the carbonyl compound in suitable solvents was mentioned.[4]

In 1948, Rothe[4,28] discovered the first naturally occurring isocyanide in the *Penicillum notatum Westling* and in the *Penicillum chrysogenum*. This compound was soon used as the antibiotic *xanthocillin* **5a**. Later Hagedorn and Tönjes[29] prepared its *O*,*O*′-dimethylether of *xanthocillin* **5b** by dehydrating its N,N′-diformylamine with phenylsulfonylchloride in pyridine (Scheme 1.2). Since



5a: R = H
5b: R = Me

Scheme 1.2 Xanthocillin.

1973 an increasing number of naturally occurring isocyanides has been found in plants and living cells.[30]

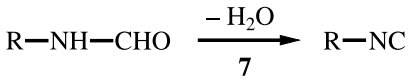
1.3 THE MODERN CHEMISTRY OF THE ISOCYANIDES

A new era of the isocyanide chemistry began in 1958 when the isocyanides became generally available by dehydrating the corresponding formylamines in the presence of suitable bases (Scheme 1.3).[4] A systematic search for the most suitable dehydrating reagent revealed early on that phosgene[31] is excellent for this purpose. Later, when phosgene transportation was not allowed anymore, it was locally produced from triphosgene.[32] Also diphosgene[33] and phosphorus oxychloride,[4] can be used, particularly in the presence of di-isopropylamine.[34] Baldwin et al.[35] prepared naturally occurring epoxy-isocyanides from the corresponding formylamines by dehydrating the latter with trifluoromethyl sulfonic acid anhydride in the presence of di-isopropylamine.

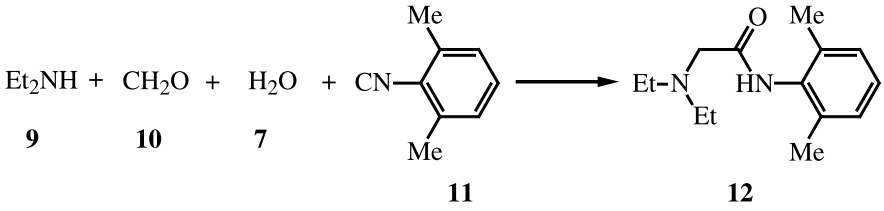
In the 1971 book *Isonitrile Chemistry*[3] 325 isocyanides were mentioned, and almost all of them had been prepared by dehydration of formylamines.

After some model reactions, Ugi et al.[3a–d] accomplished a new way of preparing Xylocaine® by one of the first U-4CRs. In 1944 Xylocaine **12**[36] (Scheme 1.4) was introduced by the A. B. Astra company in Sweden, and since then Xylocaine has been one of the most often used local anasthetics, particularly by dentists. In its early period, A. B. Astra patented 26 chemical methods of preparing **12**.

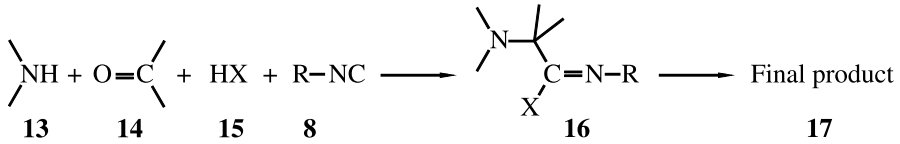
In January 1959, Ugi and co-workers decided to prepare **12** from diethylamine **9**, formaldehyde **10**, and 2,6-xylylisoxcyanide **11**. Initially they considered this as a variation of the Mannich reaction.[10] In their first experiment they noticed that this reaction is so exothermic that an immediate mixing of the educts can initiate an explosion,[3,37] and it was realized that this reaction was in reality a 4-component reaction in which water **7** also participates.



Scheme 1.3 General formation of isocyanides.



Scheme 1.4 Four-component reaction of Xylocaine®.



Scheme 1.5 The Ugi reaction.

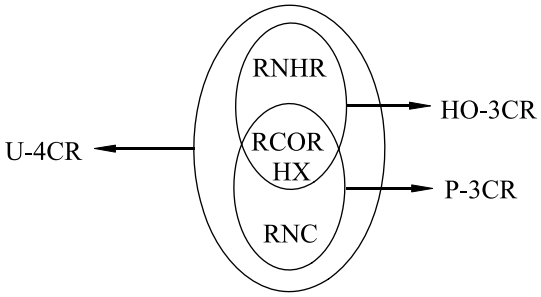
During the first month of this experiment, it was realized that this reaction is extremely variable. Thus, diverse amines (ammonia, primary and secondary amines, hydrazine derivatives, hydroxylamines) **13**, carbonyl compounds (aldehydes, ketones) **14**, acid components **15** or their anions (H_2O, $Na_2S_2O_3$, H_2Se, R_2NH, RHN-CN, HN_3, HNCO, HNCS, RCO_2H, RCOSH, $ROCO_2H$, etc.), and the isocyanides **8**[3,4,38] could form the α-adducts **16** that rearrange into their products **17** (Scheme 1.5).

Since 1962, this reaction has been called the Ugi reaction,[4a] or it is abbreviated as the U-CC,[38a] or as the U-4CR.[38b] The U-4CR can formally be considered to be a union,[39] 4CR = HO-3CR ∪ P-3CR **18** (Scheme 1.6), of the HO-3CR and the P-3CR that have in common the carbonyl compounds and acids, while the HO-3CR also needs an amine and the P-3CR an isocyanide.

In each type of chemical reaction, the skeleton of the product is characteristic, and only its substituents can be different, whereas in the U-4CR and related reactions of the isocyanides the skeleton of the products can also include different types of amines and acid components. This is illustrated by the eight skeletally different products in Scheme 1.7. Besides these compounds, many other types of compounds also can be prepared by the U-4CR.

Ordinary chemical reactions have their "scopes and limitations" for various reasons. Many sterically crowded products cannot be formed by conventional syntheses, but they can still be prepared by the U-4CR. Thus, the product **22**[40] can be formed only by the U-4CR, (Scheme 1.8).

The U-4CR forms its products by less work and in higher yields than other syntheses. The U-4CR is nowadays one of the most often used chemical reaction



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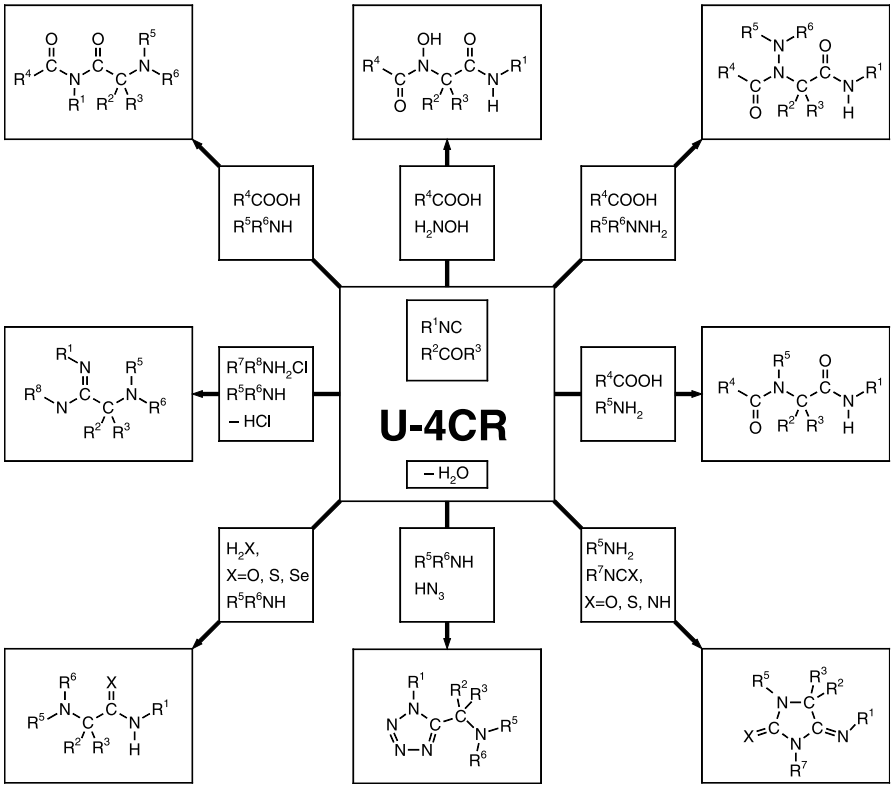
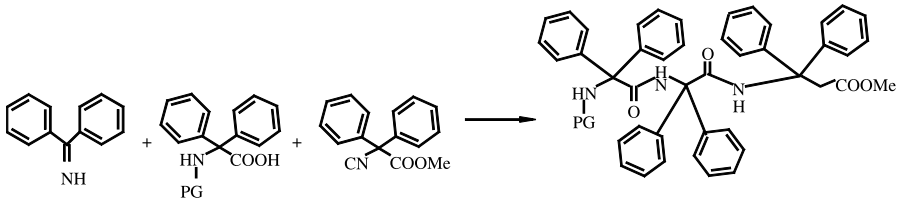
Scheme 1.6 The U-4CR as a union of the HO-3CR and the P-3CR.



Scheme 1.7 The wide variability of the U-4CR.

for the formation of chemical libraries. These libraries had already been proposed in 1961 (Ref. 3, p.149; Ref. 41), but only in the 1980s the chemical industry has recognized the advantages of the libraries.[5,42,43]

In ordinary reactions where two educts participate, 10 different components of each educt type can form 100 constitutionally different products. The U-4CR can form 10,000 different products when 10 different starting materials of each type of educt[44] are involved. In this way, libraries of an extremely high number



19 **20** **21** **22**

Scheme 1.8 Synthesis of a sterically extremely hindered product by the U-4CR.

of products can be formed via the U-4CR. Combined with other combinatorial methods, the search for new desirable products can thus be accomplished particularly well.

A product of the U-4CR is only formed in a good yield and purity if the optimal reaction conditions are used. The U-4CR proceeds faster and in a higher yield, when the amine component and the carbonyl compound are precondensed, and the acid component and the isocyanide are added later.[44] Very often methanol or trifluoroethanol are suitable solvents, but sometimes a variety of other solvents can be used as well. Furthermore, the sequence of the educts and their concentrations must be optimal and a suitable temperature of the reaction must be used. In many cases, the U-4CR can be improved by a catalyst.[1,45]

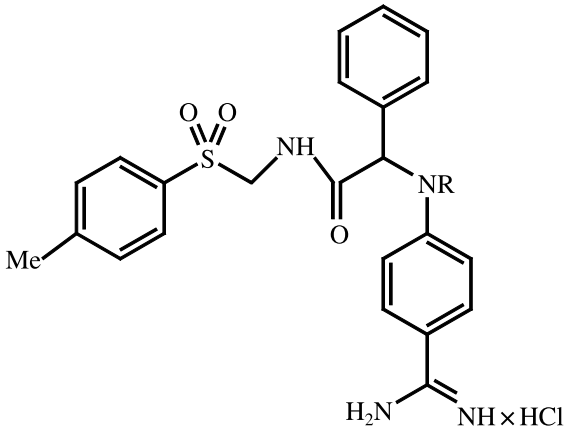
In a special case, the reaction mechanism of the U-4CR was investigated.[3,44,46] The aldehyde and chiral amine were precondensed into the Schiff-base isobutyraldehyde-(*S*)-α-phenylethylamine that was reacted with benzoic acid and *tert*-butylisocyanide in methanol at O°C. In one series of experiments, the dependence of the electrical conductivity of this Schiff-base and the carboxylic acid was determined, and in a second series of experiment, the relation between the educt concentrations and the ratio of diastereoisomeric products caused by competing different stereoselective U-4CRs was investigated. The ratio of the diastereomeric products was determined by their optical rotations.[44] The large collection of numerical values of these experimental data were evaluated by a mathematically based computer program. It was found that four pairs of stereoselective processes compete and, depending on the concentrations of the educts, one or the other diastereomeric product is preferentially formed. This knowledge made it generally possible to find the optimal conditions of the U-4CR by fewer experiments than usual.

Rather early it was recognized how much easier natural products and related compounds can be prepared by the U-4CR,[1,4] but the advantages of searching for new desirable pharmaceutical and plant-protecting compounds became evident only during the last few years, when industry began to produce the U-4CR products.[1,42]

For a whole decade a research group at Hofmann-LaRoche AG tried, without success, to find suitable thrombine inhibitors by the coventional methods. But only in 1995 Weber et al.[47] discovered two such desired products, **23a** and **23b** (Scheme 1.9), when they used libraries of 4-CR products for their systematically planned search, which also included mathematically oriented methods.

Recently, the Merck Research Laboratory demonstrated an important example.[48] Initially the HIV protease inhibitor Crixivan™ (MK 639) **29** (Scheme 1.10) could not be prepared very well by a complicated conventional multistep synthesis, but **29** became available when it was prepared by an easier synthesis, whose essential step was accomplished by a U-4CR.

Park et al.[49] used U-4CR libraries to prepare Ras-Raf protein-binding compounds like **30** that are active against HIV. The patented product **31** has been formed by Lockhoff[50] at the Bayer AG using a U-4CR of four different protected glucose derivatives that were later deprotected. The product **32** of



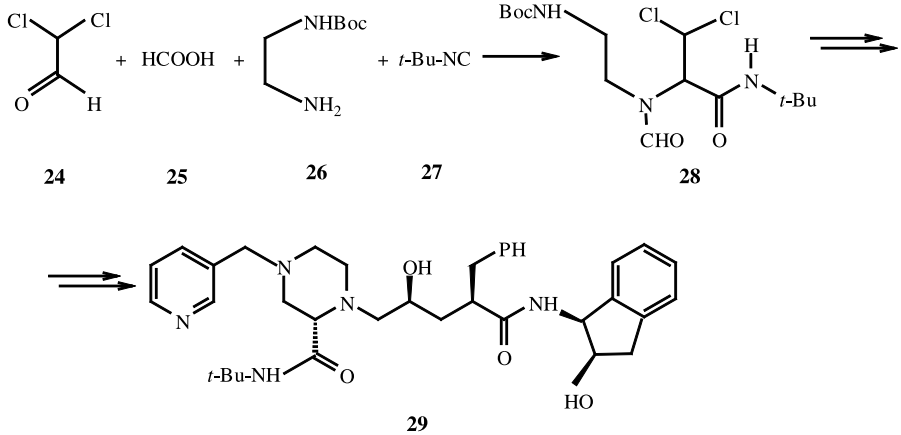
23 (a: R = H)
(b: R = *p*-hydroxy-benzoyl)

Scheme 1.9 Thrombine inhibitors by Weber et al.

Dömling et al.[51] can be prepared very easily by the U-4CR. This compound is related to the PNA compounds of Nielsen.[52]

Many cyclic products have been formed by U-4CRs from multifunctional educts. This is illustrated here by a few examples (Scheme 1.12).

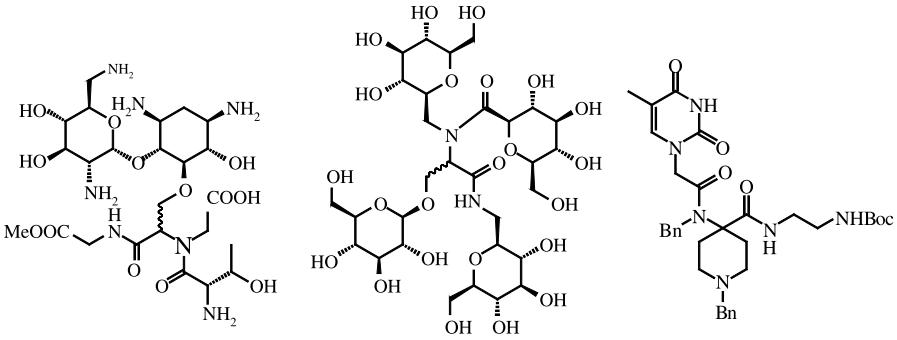
The synthesis of the penicillin-related compound **39**, introduced in 1962, begins with an A-4CR of **37a**, which is hydrolized into **37b**. This undergoes a U-4CR with isopropyl-isocyanide **38** and forms **39**.[53] During the following decades, a large variety of antibiotically active β-lactam derivatives was produced.[54] Recently **42,** compound **43**, and one of its stereoisomers were stereospecifically prepared by U-4CRs.[55]



24 **25** **26** **27** **28**

29

Scheme 1.10 Synthesis of Crixivan™ (MK 639).



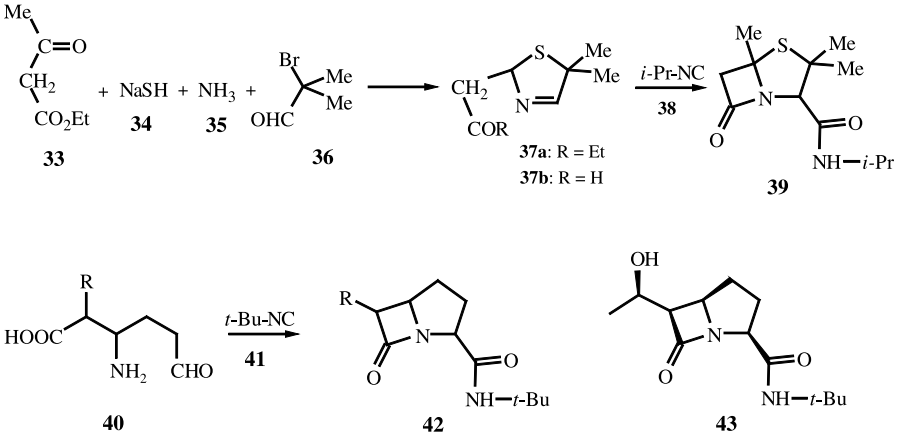
30 **31** **32**

Scheme 1.11 Biologically active compounds synthesized via U-4CR.

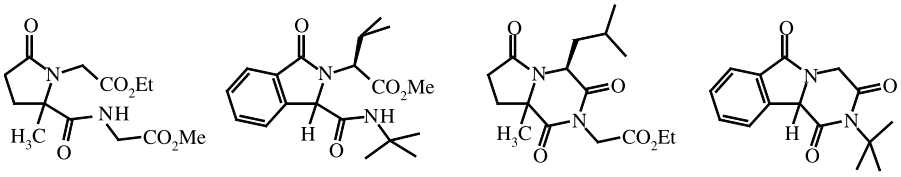
A variety of cyclic products have been prepared from educts containing carbonyl as well as carboxylic groups. Thus, Hanusch-Kompa and Ugi[56,57] prepared a large number of five-membered cyclic gamma-lactam compounds like **44** from levulinic acid. Other carbonylic acids can lead to compounds like **45**, which is made from phthalaldehyde acid, valine methylester, and *tert*-butylisocyanide. The products like **46** and **47** can result from the U-4CR and further cyclization.

In addition, the six- to eight-membered lactams like **48**, **49**,[58] and **50**[59] have been formed from amines, carbonyl-carboxylic acids, and isocyanides (Scheme 1.14).

Product **56** (Scheme 1.15) with a particularly complicated structure was prepared by the U-4CR of **51**–**54**, followed by a few further steps.[60]

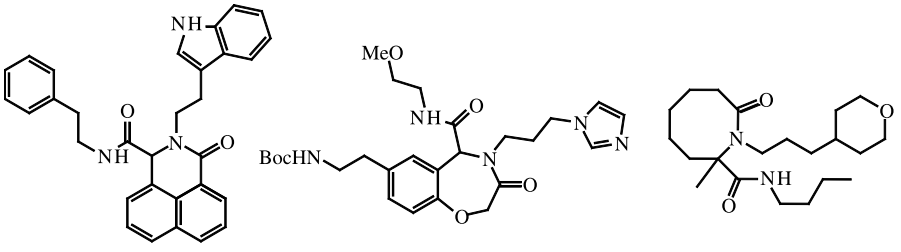


Scheme 1.12 U-4CR products of multifunctional educts.



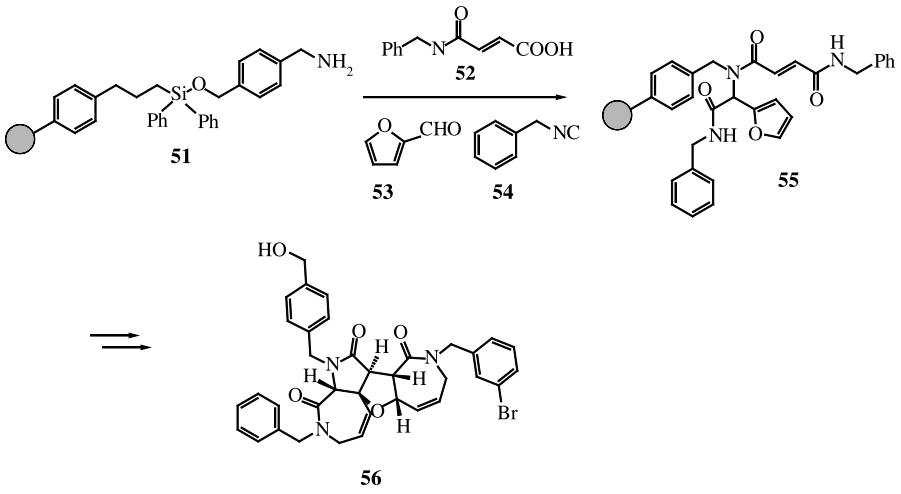
44 **45** **46** **47**

Scheme 1.13 U-4CR products from carbonyl groups containing carboxylic acids.



48 **49** **50**

Scheme 1.14 Six- to eight-membered lactams formed via U-4CR.



51 **52** **53** **54** **55** **56**

Scheme 1.15 Solid-phase synthesis of a polycyclic ring system employing a U-4CR.

1.4 STEREOSELECTIVE U-4CR

After the U-4CR had been introduced, it was soon recognized that this reaction can form diastereomeric products from chiral amine components,[61,62] for example, chiral α-ferrocenyl-alkylamines.

As the latter were not easily accessible by chemical synthesis at that time,[44] new methods of preparing these ferrocene derivatives were developed and introduced in 1969.[63] It was then proved that the U-4CRs of chiral α-ferrocenyl-alkylamines can form diastereomeric α-aminoacid derivatives stereoselectively, and it was further shown that after the reaction the α-ferrocenyl groups of the products can be replaced by protons, thus resynthesizing the chiral α-ferrocenyl-alkylamines simultaneously.[44] Later, the development of this ferrocene chemistry was given up since such syntheses cannot form the products in sufficient quantity and stereoselective purity.[64]

In 1988 Kunz and Pfrengle[65] introduced the preparation of chiral amino acid derivatives by the U-4CR in the presence of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine, **57**, in the presence of $ZnCl_2$-etherate as catalyst. They obtained excellent stereoselectivity and high yields of their products. One of the disadvantages of such U-4CRs is that only formic acid can be used as the acid component, and the auxiliary group of the products can only be removed by half-concentrated hot methanolic HCl.

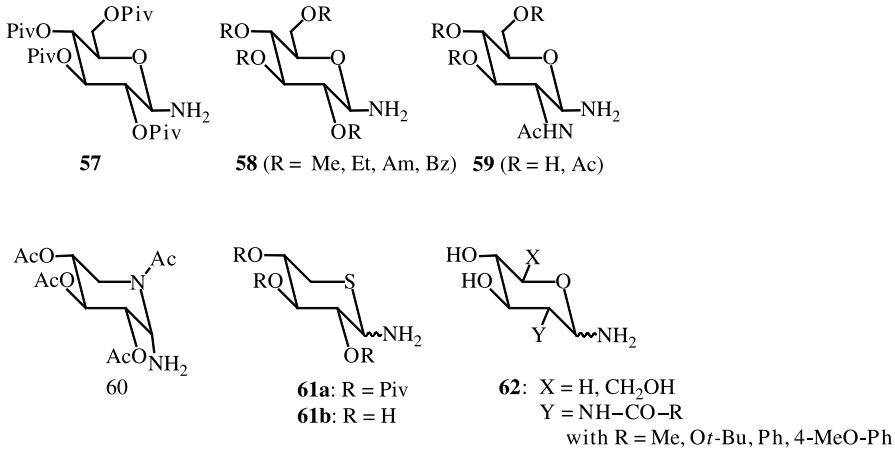
A few years later Goebel and Ugi[66] formed α-aminoacid derivatives by the U-4CR with tetra-*O*-alkyl-1-glucopyranosylamines, **58**, where any carboxylic acid component can participate. Lehnhoff and Ugi[67] used the U-4CR with 1-amino-2-deoxy-2-*N*-acetylamino-3,4,6-tri-*O*-acetyl-β-D-glucopyranose, **59**, whose large variety of products could be formed stereoselectively in excellent yields. The desired selective cleavage of the auxiliary groups of these products was equally unefficient.

Zychlinski[68] prepared 1-amino-5-deoxy-5-acetamido-2,3,4-tri-*O*-acetyl-β-D-glucopyranose **60** by a synthesis of 11 steps. This amine component undergoes the U-4CRs very well and the products are cleavable by water, but unfortunately they are not very stable.

Ross and Ugi[43] prepared 1-amino-5-deoxy-5-thio-2,3,4-tri-*O*-isobutanoyl-β-D-xylopyranose **61a** from xylose via the 5-desoxy-5-thio-D-xylopyranose. The U-4CRs of this amine form α-aminoacid derivatives stereoselectively and in excellent yields. These products have the advantage that their products are stable and their auxiliary group 5-desoxy-5-thio-D-xylopyranose can be cleaved off selectively by mercury(II) acetate and trifluoroacetic acid. The expected steric structure of the corresponding U-4CR product was confirmed by X-ray measurement.[69]

Since Ugi is now an emeritus and he and his co-workers cannot continue their experimental studies, we propose that the analog 1-amino-5-desoxy-5-thio-D-xylopyranose **61b** should be prepared and be used as a reagent of U-4CRs. It has a good chance to form stereoselectively high yields of products whose auxiliary group can be selectively removed.

In 1985 Kochetkov et al.[70] introduced the preparation of 1-amino-carbohydrates from xylose, glucose and 2-acetylamino-glucose just by adding ammonia, and later they improved the preparation of pyranosylamines by using additional ammonium carbonate.[71]



57 **58** (R = Me, Et, Am, Bz) **59** (R = H, Ac)

60

61a: R = Piv
61b: R = H

62: X = H, CH_2OH
Y = NH–CO–R
with R = Me, O*t*-Bu, Ph, 4-MeO-Ph

Scheme 1.16 Chiral amino carbohydrates employed in the U-4CR.

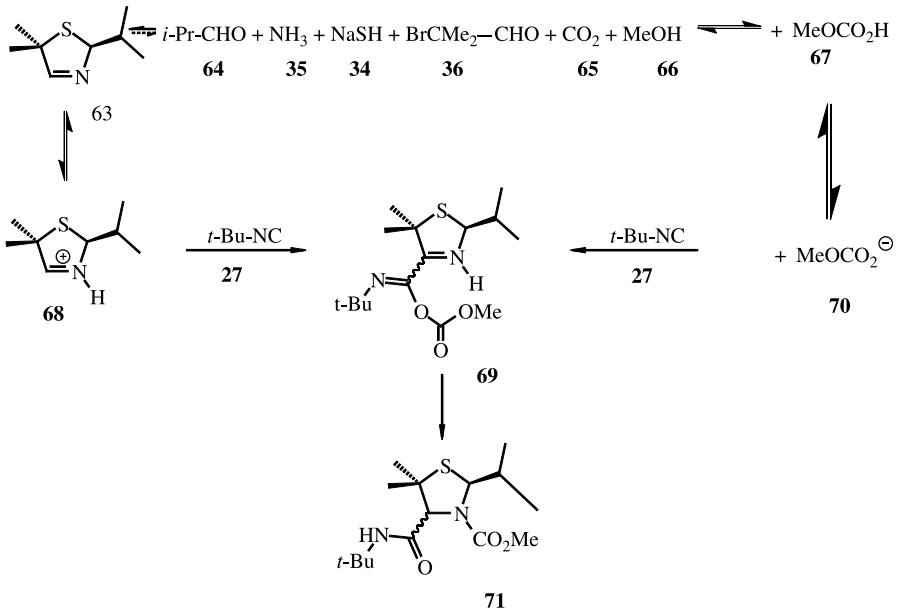
Drabik et al.[45] prepared these and additional 1-amino-carbohydrates, **62**, which were used as the amine components of the U-4CRs. Thus, α-aminoacid derivatives could be prepared stereoselectively in good yields. The stereoselectivity and yields resulted especially well if 0.1 gram equivalent (eq.) $ZnCl_2-OEt_2$ or $CeCl_3-7H_2O$ or $ZrCl_4$ were used as catalysts. Among these, $CeCl_3-7H_2O$ had a particularly good influence, so that 99% yields and stereoselectivities of 99% d.e. can result.

The auxiliary carbohydrate parts of the products could be removed only moderately. The most efficient cleavages were achieved when the U-4CR products of the amine component **62** were treated with 1 M HCl in methanol at 40°C for 19 h. In that case, yields up to 30% could be achieved; for Y = NH-CO-4-MeOPh in compound **62**, the cleavage rate could be increased up to a yield of 46%.

1.5 THE UNIONS OF THE U-4CR AND FURTHER REACTIONS

Already in the early days of the U-4CR, several types of 5CRs were found.[3,72] It was also observed long ago that an autoxydizing 6-component reaction of two isocyanides took place besides the main U-4CR,[73] and the structure of one of these by-products was determined by an X-ray measurement.[74] The reaction mechanism of such autoxydation was determined[75] by the assistance of the computer program RAIN.[76] At that time it was not yet known that the MCRs of isocyanides with more than four educts proceed by different reaction mechanisms.

The new era of isocyanide chemistry was determined by two aspects. First, it was the formation of products by MCRs with high numbers of educts and second, the recently initiated search for new desirable products in libraries of MCR



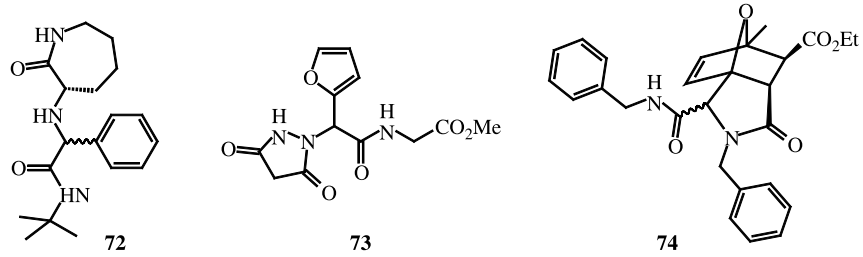
Scheme 1.17 The first 7-CR.

products.[1] In 1995, the chemical industry began to search for new compounds in the libraries of products formed by the U-4CR and related reactions.

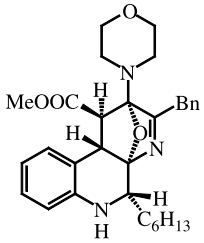
Using this new technology, a single chemist can now form more than 20,000 new compounds a day, whereas before a good chemist could accomplish up to 10,000 syntheses in the 40 years of his or her professional life. MCRs are especially suitable for the formation of libraries, since they have the big advantage that their products can be prepared with a minimum of work, chemical compounds and energy, and in essentially higher yields than by conventional methods.

In 1993 the first MCR composed of seven educts was introduced,[77] and it was soon recognized that such higher MCRs are usually unions[39] of the U-4CR and additional reactions.[38] In the first 7-CR, the intermediate **63** was formed by an A-4CR and underwent with the equilibrating product **67** the α-addition of the cations and ions onto the isocyanide **27**. Finally, this α-adduct, **69**, rearranges into the final product, **71** (Scheme 1.17).

The variety of educts and products of the higher MCRs is illustrated here. Product **72** (Scheme 1.18) is formed from the five functional groups of lysine, benzaldehyde, and tert-butylisocyanide.[78] The synthesis of **73** is achieved with hydrazine, furanaldehyde, malonic acid, and the isocyano methylester of acetic acid,[57,79] compound **74** results from the reaction of benzylamine, 5-methyl-2-furanaldehyde, maleic acid mono-ethylester, and benzylisocyanide.[80] Zhu et al.[81] prepared a variety of related products, such as, **75**, from *O*-amino-methyl cinnamate, heptanal, and α-isocyano α-benzyl acetamides.

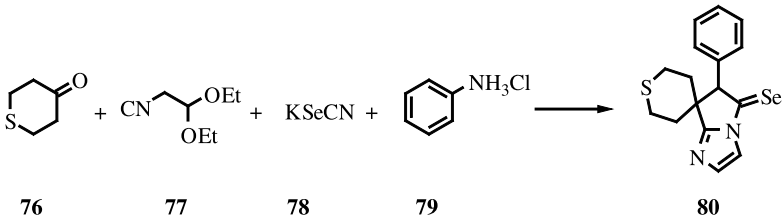


72 **73** **74**

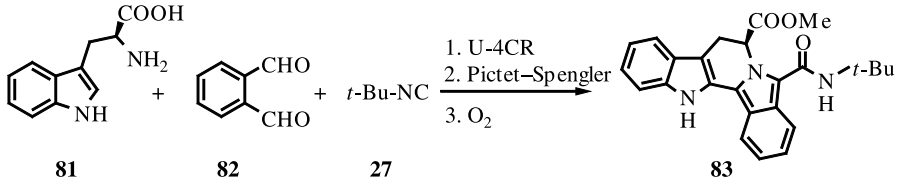


75

Scheme 1.18 Products of higher MCRs.

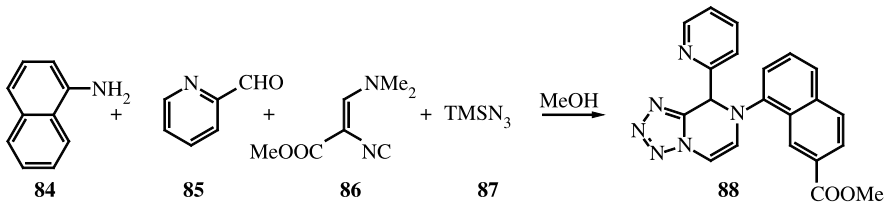


76 **77** **78** **79** **80**



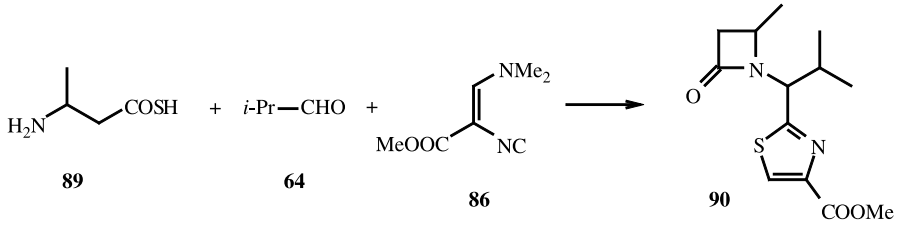
81 **82** **27** **83**

Scheme 1.19 Polycyclic products of higher MCRs.

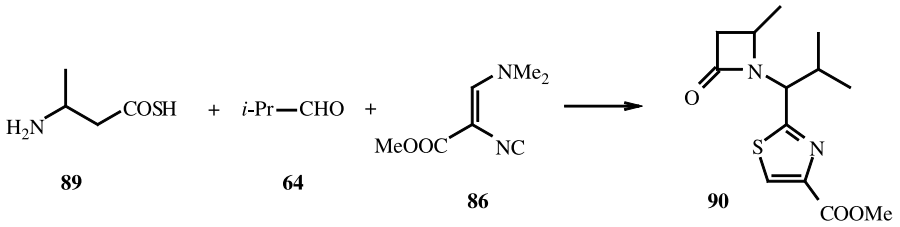


84 **85** **86** **87** **88**

Scheme 1.20 Heterocycle formation by MCRs.



Scheme 1.21 MCR employing a thioacid.



Scheme 1.22 Examples of MCRs with up to nine reacting functional groups.

In the last decade, Bossio et al.[82] have formed cyclic products of many different types by using a variety of new MCRs. Thus, **80** was made from **76**–**79** (Scheme 1.19). Recently, Dömling and Chi[83] prepared **83** from **81**, **82**, and **27**, and synthesized similar polycyclic products from other α-aminoacids with **82** and **27**.

In 1979, Schöllkopf et al.[84] formed α-isocyano-β-dimethylamino-acryl methyl esters **86**, and Bienaymé prepared many similar isocyanides,[85] which can undergo a variety of heterocycles, forming reactions like the synthesis of **88**[86] from **84**–**87** (Scheme 1.20).

Dömling et al.[87] made react β-amino butyric thioacid, **89**, the isobutyraldehyde **64**, and **86** into the product **90**, which simultaneously contains a ß-lactam group and a thiazole system.

A variety of MCRs with seven to nine functional groups of several pairs of educts can be carried out, as is illustrated by the four subsequent reactions.[88–90] (Scheme 1.22).

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