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Recent progress in the chemistry of multicomponent reactions*

Ivar Ugi

Technical University of Munich, Department of Organic Chemistry, Chair 1, Lichtenbergstrasse 4, D-85747 Garching, Germany

Abstract: The chemistry of multicomponent reactions (MCRs) and isocyanides belongs to three periods: In the century 1859–1958, isocyanide chemistry was moderately active and was separate from the classical name reactions of the MCRs. In the next period, isocyanides became well available, and MCRs of isocyanides became the most variable way of forming chemical compounds. The year 1993 began a new era of the formation and investigation of the products and the libraries of the Ugi reaction (U-4CR) and higher MCRs of the isocyanides. This chemistry is primarily accomplished in the industrial search and preparation of new pharmaceutical and plant-protecting products.

FIRST CENTURY OF THE CHEMISTRY OF ISOCYANIDES AND MCRs

Besides the usual multistep syntheses, an increasing number of organic chemical compounds are formed by multicomponent reactions (MCRs) that convert more than two educts directly into their products by one-pot reactions. In contrast to the multistep syntheses, the MCRs need minimal work, and they have often quantitative yields.

The first MCRs were accomplished in 1838 when Laurent and Gerhardt [1] formed the "benzoylazotide" from bitter almond oil and ammonia via benzaldehyde, hydrogen cyanid. The chemistry of the MCRs officially began twelve years later, when Strecker [2] introduced the general formation of α-aminocyanides from ammonia, carbonyl compounds, and hydrogen cyanide. The preparation of heterocyclic compounds by MCRs was introduced in the early 1880s [3]. Since then, many "name reactions" of MCRs were developed. This ended in 1960, when Hellmann and Opitz [4] published the *α-Aminoalkylierung* book where they demonstrated that all of these classical name reactions are α-aminoalkylations of nucleophiles, including the preparations of heterocyclic products by MCRs that are α-aminoalkylations and subsequent ring-forming reactions of further bifunctional educts.

In 1859, the chemistry of the isocyanides began when Lieke [5] formed the allyl isocyanide from allyl iodide and silver cyanide. Eight years later, Gautier [6] formed alkylisocyanides thus generally, and at the same time Hofmann [7] introduced the formation of isocyanides from primary amines, chloroform, and potassio hydroxyde. For a whole century, only twelve isocyanides had been produced [8].

The chemistry of isocyanides is fundamentally different from the rest of organic chemistry, since they are the only chemical compounds with divalent carbon atoms C^{II}, and all of their chemical reactions correspond to conversions of the divalent carbon atoms C^{II} into the tetravalent carbon atoms C^{IV}.

In 1921, Passerini [8,9] introduced the first MCRs of the isocyanides. They react with carboxylic acids and carbonyl compounds into the acyloxy-carbonamides. This first century of isocyanide chemistry contained important progress, but overall was a rather empty part of chemistry.

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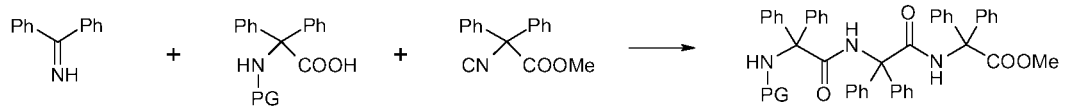
AN ERA OF PROGRESS IN THE CHEMISTRY OF ISOCYANIDES AND MCRS

In 1950, the naturally occurring diisocyanide Xanthocillin [12] was found that was later used as an antibiotic. Its dimethyl ether was prepared by Hagedorn and Tönjes [11] in 1956 by dehydrating its diformyamine by p-tolylsulfochloride in the presence of pyridine. Later, many isocyanides were found in living cells. Scheuer *et al*. [13] have been particularly active and successful in the chemistry of the naturally occurring isocyanides.

In 1958, the isocyanides became generally well available [18,14], and shortly after, Ugi *et al*. [15] introduced the four-component reaction of the isocyanides, which is, since 1962, referred to as the Ugi reaction (U-4CR) [16]. The U-4CRs are one-pot reactions of amines, carbonyl compounds, acids, and isocyanides that form products from any educts while other chemical reactions and MCRs have "scopes and limitations" [16]. This is illustrated by the sterically hindered **4** that can also be formed by a U-4CR [17], whereas **4** cannot be prepared by any other method.

Many natural products have been formed by the U-4CR [16], and it was early recognized that cyclic products can be formed by the U-4CR [18b]. Thus, a great variety of β-lactam antibiotics and relate compounds has been produced by the U-4CR [19].



Scheme 1

Since 1963, stereoselective U-4CRs were developed [20]. Particularly, stereoselective syntheses of peptide derivatives by U-4CRs of suitable chiral amine components were developed. The U-4CR of chiral α-ferrocely alkylamine derivatives did not proceed sufficiently well [21]. Kunz and Pfrengle [22] introduced the formation α-aminoacid derivatives by stereoselctive U-4CRs with *O*-pivalyl-1-amino-carbohydrates, which had many preparative advantages, but they were still not yet the suitable components of peptide syntheses by the U-4CR. Recently, Ugi and Ross [23] introduced *O*-acylated 1-amino-carbohydrate derivatives whose endocyclic oxygen was replaced by sulfur. Thus peptide derivatives can stereoselectively be formed by the U-4CR, and their products can be cleaved in the desired way under mild conditions.

Three types of MCRs are known [10]. Type I MCRs are an equilibrium between the educts, intermediates, and final products, whereas Type II MCRs consist of equilibria between educts and intermediates whose final product is in practice irreversibly formed. Type III MCRs are sequences of practically irreversible subreactions that proceed from the educts to the products.

The classical α-aminoalkylations of nucleophiles are Type I MCRs. The formation of heterocyclic products by MCRs and the MCRs of the isocyanides belong to Type II. Type III MCRs are rare in preparative chemistry, but the biochemical formations of products are usually Type III MCRs [10].

MODERN CHEMISTRY OF THE MCRs AND THEIR LIBRARIES

Already in 1961, Ugi and Steinbrückner [18a] described the libraries of U-4CR products, and this was mentioned again in 1971 [8, p. 149]. For many decades nobody had been interested in libraries. In 1982, Furka [24] formed peptide libraries by the solid-phase method of Merrifield [25], and since then this was increasingly applied. Libraries of other compounds were subsequently also formed by multistep solid-phase procedures [26].

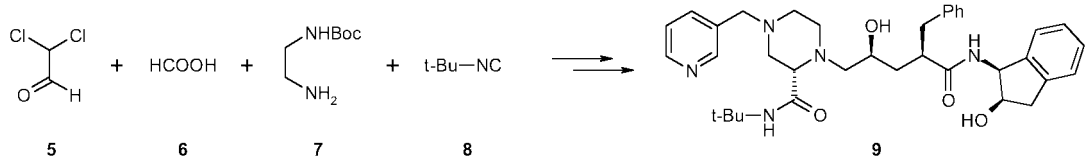
In 1995, Armstrong *et al.* [27] and in the Hofmann LaRoche AG Weber *et al.* [28] published the first industrial libraries of U-4CR products; the latter group had then found two Thrombine inhibitors,

whereas the search for such products by the then conventional methods was not successful for a decade. A still-increasing number of industrial companies began to produce and to investigate the libraries of the U-4CR products and related compounds. Nowadays, the search for new pharmaceutical and plant-protecting compounds is accomplished by forming libraries of up to 20 000 and more different compounds in one day by a single person.

This new era of the chemistry of the U-4CR and related compounds began already in 1993 when Dömling and Ugi [29] formed the product of an MCR of seven different educts as a union [30] of the U-4CR with an Asinger reaction and an equilibrium between methoxy-carboxylic acid and carbon dioxyde in methanol.

In the new era of MCR chemistry [31], besides the libraries also many new types of products have been introduced.

The Merck Research Laboratory [32] had initially tried to produce and sell the HIV protease inhibitor Crixivan™ (MK 639) **9,** but they could not prepare this compound sufficiently well by a complicated conventional multistep synthesis. However, **9** became available when it was prepared by a synthesis with an essential step of the U-4CR.



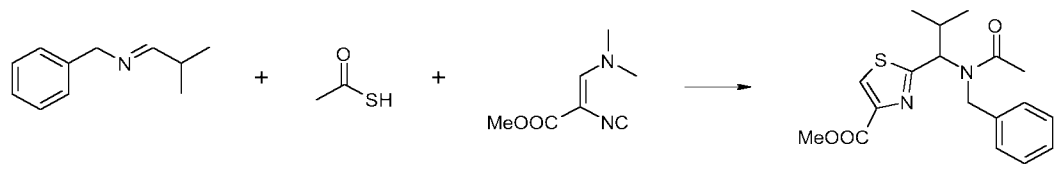
5 **6** **7** **8** **9**

Crixivan (MK 639)

Scheme 2

A variety of new reactions of isocyanide were introduced by Bossio *et al*. [33], and Curran *et al*. [34] introduced some progress in the chemistry of the isocyanides. A U-4CR of four different carbohydrate derivatives as their educts was introduced by Lockhoff [35].

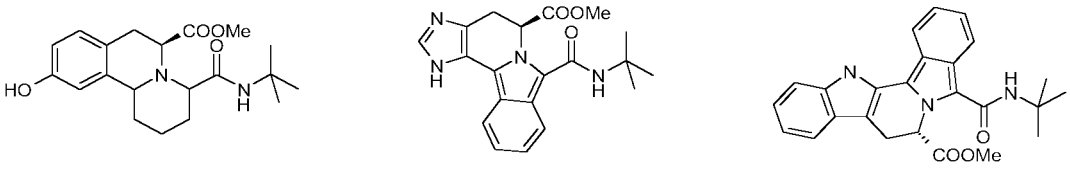
A new way of preparing complicated thiazole derivatives **13** by one-pot reactions was introduced by Heck and Dömling [36].



10 **11** **12** **13**

Scheme 3

The alkaloid-related compounds **14**–**16** can be formed by the one-pot reactions of tyrosine, histidine, or tryptophane with phthalic dialdehyde and *tert*-butylisocyanide. Dömling and Chi [37] prepared a variety of alkaloid-related compounds by U-4CRs of α-aminoacids, dialdehydes, and *tert*-butyl isocyanide.



14 **15** **16**

Scheme 4

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