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Chemistry of the isocyanides and their multicomponent reactions, including their libraries – the initiatives of Ivar Ugi

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In remembrance of Ivar Ugi

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The chemistry of the isocyanides began in 1859 when Lieke had prepared allyl isocyanide as the first isocyanide [1]. For the following century only 12 isocyanides were known and rather few types of reactions had been described. Thus for a whole century, from 1859 to 1958, isocyanides were not readily available, and the chemistry of the isocyanides remained a rather empty part of organic chemistry [1].

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In 1958 Ugi and his co-workers introduced various methods to form isocyanides by dehydrating formylamines, and from then on the isocyanides were well available. Subsequently the extremely variable preparative four component reaction of the isocyanides (U-4CR) was introduced. Under suitable reaction conditions, these one-pot reactions require generally much less work and form higher yields of products than the usual multistep syntheses. In 1993 also higher multicomponent reactions (MCRs) were introduced as unions of the U-4CR and further reactions with up to nine educts. Already in 1961 libraries of U-4CR products were introduced, but in industry this chemistry became one of the most often used methods for the search for desirable new products only many decades later.

In principle, all chemical reactions are equilibria between one or two educts and their products, but in practice the preferred chemical reactions form their products irreversibly. Optimal reactions can form quantitative yields of products if no competing reaction takes place. Usual syntheses from three or more educts are sequences of reaction steps. After each step the product must be isolated and purified and with each step the amount of work increases and the yield decreases.

Besides the usual organic chemistry, a rapidly increasing number of chemical compounds is prepared also by the one-pot MCRs, which have the advantage that their products are often formed under almost physiological conditions, and high yields of products are formed without essential preparative work [1, 2]. However, very often high yields of products are only formed under optimal reaction conditions, and this can require research work.

The chemistry of the isocyanides is profoundly different from the rest of organic chemistry, because the functional group of the isocyanides is the only one that contains a divalent carbon atom C^{II}, and their practically irreversible reactions correspond to exothermic conversions of the C^{II} into the C^{IV} [1].

In the usual organic chemistry only a few MCRs are known, and each reaction produces compounds with a similar skeleton and only different substituents, whereas in the chemistry of the isocyanides a much greater variation of MCRs is known. In the U-4CRs and related reactions the skeletons and the substituents can differ. Thus in the chemistry of the isocyanides more different educts and products can participate than in the conventional reactions.

Since 1958 when Ugi and his co-workers introduced new methods of preparing the isocyanides by dehydrating formylamines [1–3] the isocyanides are well available. Already in the 1971 volume of *Isonitrile Chemistry* [1] 325 isocyanides were mentioned, and today approximately 3000 isocyanides are known.

In 1959 Ugi and co-workers introduced the U-4CR of the isocyanides [1, 4, 5], which is since 1962 quoted as the Ugi reaction [5]. The U-4CRs of various types of amino compounds, aldehydes, ketones, and various types of acids and isocyanides form their products just by mixing the educts. The U-4CR is by orders of magnitude more variable than any other chemical reaction or classical MCR [6]. The yields of the U-4CRs are usually much higher than of other ways of forming these products. However, the U-4CR forms high yields of pure products only if optimal reaction conditions are used. Until 1995 the U-4CR was moderately often used, but since then industry has formed more chemical compounds by the U-4CR than by the whole previous chemistry [6]. Thus a single person can produce 20 000 or more new compounds in a single day, assisted by automated equipment.

Shortly after the introduction of the U-4CR, Ugi and his co-workers began to study stereoselective U-4CRs of chiral amine components [1, 7–9]. In 1967 Ugi and the mathematician Kaufhold determined the reaction mechanism of a stereoselective U-4CR by using a combination of experimental and mathematically oriented computer assisted methods. Since then stereoselective U-4CRs can be accomplished more efficiently [8, 9].

In 1969 chiral ferrocenyl-alkylamines were introduced for the preparation of chiral α-aminoacid derivatives by stereoselective U-4CRs [9]. After the reaction the auxiliary ferrocenyl-alkyl group could be removed selectively and the chiral ferrocenyl-alkylamine re-synthesized. These results did not develop into a generally advantageous method of preparing α-aminoacid, since not all of its steps proceed sufficiently well.

In 1988 Kunz et al. [10, 11] investigated the stereoselective U-4CR with O-acyl-1-aminocarbohydrates, but only formic acid reacted well as the acid component, and the products could be cleaved only unselectively by hot concentrated hydrochloric acid.

Some years later Ugi and co-workers began to search for a suitable amine carbohydrate derivative that would allow the desirable stereoselective types of U-4CR and the subsequent selective removal of the auxiliary group from the product. After testing many amine components of amine carbohydrates in the U-4CR, it was found that α-amino-5-deoxy-5-thio-2,3,4-tri-O-isobutanoyl-β-D-xylopyranose and its enantiomer fulfill all requirements of the stereoselective U-4CR. The products are selectively cleavable under mild conditions, and after the reaction, besides the desired product also its initial amine component can be resynthesized. Although chiral pharmaceutical products are now needed, the industry has not yet started the production of chiral compounds from the stereoselctive U-4CRs. Since 1993 Ugi and his co-workers began to form products by unions of the U-4CR with further reactions [12–14]. Thus five to nine starting materials can directly be converted into their products [2, 6, 15].

In 1961 [16] and again in 1971 [1], Ugi had also described libraries of U-4CR products, but for many decades nobody realized the potential advantages of simultaneously producing many different products. However, in 1982 Furka [17] began to prepare the solid phase multistep libraries of peptides, and then many companies started the investigation of such libraries. Later also related multistep solid phase libraries were prepared. However, after some years the limitations of the solid phase multistep libraries were recognized, and since 1995 the chemical industry admits the advantages of searching for new desirable products from libraries of products formed by the U-4CR and related one-pot reactions in solid and liquid phases [6].

Also large amounts of many desirable products can be prepared in high yields by the U-4CR – 10 of the 20 most often sold American pharmaceutical products can be formed by the U-4CR – and a very wide variety of pharmaceutical and plant protecting compounds can particularly well be found from libraries of U-4CR products.

The local anaesthetic Xylocian™ of the AB Astra [2] was one of the first products that was prepared by the U-4CR. In the last decade many other companies have developed about 30 similar anaesthetic compounds, which can particularly well be prepared by the U-4CR. Recently the Merck Research Laboratory [18] found that the HIV inhibitor Crixivan™ (MK-639) has excellent pharmaceutical properties, but first could not produce this compound in an

economically reasonable way. The introduction of the U-4CR and two further steps into the synthesis enables them to produce Crixivan™ sufficiently well and offer it on the market. For a whole decade the Hofmann LaRoche company had – without success – tried to find a thrombine-inhibitor. In 1995 Weber and the group of his co-workers in this company [19] began to search for such a product by sequences of U-4CR libraries, and within three months they found two such desirable products. Probably soon one of these products will become a commercial product.

In the last few years many companies – particularly in the USA, Switzerland, and France – are very active in the MCR field, but only very few academic groups like those of Bossio, Curran, and Schreiber [6] have recently shown activity, although the chemistry of the isocyanide MCRs is one of the few areas of chemistry where still much progress can be made.

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