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Stereoselective one-pot synthesis of α-aminoacid derivatives by four component reactions with 1-amino-carbohydrates and isocyanides

Dedicated to Prof. Mihkel Veiderma

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Abstract. For a whole century the chemistry of the isocyanides was a rather neglected part of chemistry. A new era began in 1958 when the isocyanides became well available, and a year later the four component reaction of the isocyanides (U-4CR) was introduced. A greater variety of products can be prepared by the U-4CR, which requires minimal work, and under well selected conditions almost quantitative yields of products are often formed. The U-4CR can be accomplished by just mixing the educts, and the reaction proceeds under physiology related conditions. Since 1995 the products of the U-4CR and its unions with further reactions are industrially more often used as the libraries than by other methodologies. Ways of forming chiral products by the U-4CR have been investigated for many decades, but only recently methods were developed by which suitable unprotected 1-amino-carbohydrates and related amines of the U-4CR can be found. In 1986 Kochetkov and co-workers found that 1-amino-carbohydrates can be prepared by just mixing carbohydrates and ammonium hydrogen carbonate. It was found that stereoselective syntheses of chiral products can efficiently be performed by the U-4CR of such easily available 1-amino-carbohydrates as their chiral amine components. The carbohydrate groups of its U-4CR products can selectively be removed in yields of up to 46% of its resulting compounds.

Key words: one-pot reaction, four component reaction of isocyanides, Ugi reaction (U-4CR), 1-amino-carbohydrates, stereoselectivity, α-aminoacid derivatives, selective cleavage.

THREE PERIODS OF ISOCYANIDE CHEMISTRY

The chemistry of isocyanides [1–9] began in 1859 when Lieke [10] formed allyl isocyanide from allyl iodide and silver cyanide. In 1866 Meyer [11] produced in a similar way 1-isocyano-1-desoxy-glucose. Shortly later Gautier [12] and Hofmann

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[13] introduced the early general methods of preparing isocyanides. Gautier had also tried to dehydrate the amine formates by phosphorus pentoxyde but there he could not obtain isocyanide [14], since the acidic medium immediately destroyed the isocyanide. Still, for a whole century the chemistry of isocyanides remained rather a neglected part of organic chemistry with only 12 isocyanides prepared and just a few of their reactions introduced [1]. In that period reactions of isocyanides of particular importance were the formation of tetrazole derivatives from isocyanides and hydrazoic acid developed by Oliveri-Mandala and Alagna in 1910 [15, see also 16] and the first three component reaction of the isocyanides (P-3CR) introduced by Passerini in 1921 [1, 9, 17, 18].

A new era of the isocyanide chemistry began in 1958, when the isocyanides became generally well available by dehydrating formylamines. The volume of the *Isonitrile Chemistry* [1] of 1971 already mentioned 325 isocyanide. We estimate that now more than 3000 isocyanides have been prepared [9].

In 1959 the four component reaction of amines, carbonyl compounds, acids, and isocyanides was introduced [19], which is now one of the most often used chemical reactions. Since 1962 this reaction is quoted as the Ugi reaction [2, p. 1090], or is abbreviated as the U-4CC [20], or the U-4CR [21]. In 1961 the collections of the U-4CR products were introduced as libraries [1, p. 149, 22].

If chemical compounds are prepared from more than two educts, several preparative steps must usually be accomplished, and after each step its intermediate or final product is isolated and purified. Besides this chemistry, an increasing number of chemical compounds are prepared by multicomponent reactions (MCRs) just by mixing their educts [1–9]. The educts of the MCRs are not directly converted into their products by a single step, but they correspond to collections of subreactions, whose final steps form their products. The U-4CR and related reactions are particularly often used, since their educts and products are more variable than in other reactions. The U-4CR can be accomplished by little preparative work and its products are formed in higher yields than by the conventional syntheses by multistep procedures [9]. Often the U-4CR forms only a high yield of a pure product if the optimal reaction conditions are used, and these can differ from case to case. Under other reaction conditions mixtures of products can result, and in some cases totally different types of main products are formed.

The majority of chemical reactions convert one or two educts into their desirable products. Exceptions are some solid phase reactions of three components, and it was recently demonstrated that the prefinal steps of the isocyanide MCRs are three component reactions that simultaneously undergo α-additions of cations and anions onto the isocyanides [23]. The resulting intermediate products subsequently rearrange into the final products.

Three types of MCRs are known. In MCRs of type I the educts, intermediate products, and final products equilibrate, whereas in type II the last steps of forming the products proceed irreversibly. The MCRs of type III are sequences of subreactions that proceed in practice irreversibly from the educts towards the products [3].

The year 1850 introduced the Strecker reaction [24] of type I, whereas the year 1882 introduced heterocycles forming MCRs of Hantzsch [25] and Radziszewsky

[26], which, as well as the P-3CR [17] and the U-4CR [1], are MCRs of type II. Reactions of type III [27] are rare in the preparative chemistry, but the majority of the biochemical products of the living cells are formed by MCRs of type III [3].

Higher MCRs [20, 21, 28] of up to nine educts [29] that are unions* of the U-4CR with further reactions were introduced in 1993. It was recognized that in the preparative chemistry the MCRs form only high yields of pure products, if they belong to type II [3]. Since 1995 the chemistry of the MCRs and the libraries of the isocyanides are the most often used reactions of forming chemical products and their libraries [9] in order to find thus new desirable products with pharmaceutical potential.

The recent industrial progress of the U-4CR chemistry is illustrated by a few examples. At the Bayer AG Lockhoff [31, 32] prepared a new potentially useful product of the U-4CR with four different carbohydrate derivatives as educts. In the Merck corporation a new HIV protease inhibitor *Crixivan*^{R} was initially developed by a synthesis of roughly 20 steps, but since recently this product can more efficiently be prepared by including an U-4CR and a few further steps [33].

The chemistry of the U-4CR products became industrially popular since 1995, when Armstrong [34] developed products by the U-4CRs and subsequent reactions. At the same time in the Hofmann LaRoche company Weber et al. [35, 36] introduced a combination of logical methods and the planning of sequences of U-4CR product libraries. Within a few months they were able to find two desirable products, whereas the research group of the same company had without success tried to find such a product by the classical research methods for a whole decade.

Before the chemistry of the libraries became active, roughly 20 000 000 chemical compounds had been prepared, but since then more than 100 000 000 chemical compounds have been formed. In many companies a single chemist can prepare in one day up to 20 000 and more products by their semi-automatic methods, whereas previously an active chemist could prepare up to 10 000 compounds in 40 years. Up to $(100)^2 = 10\,000$ constitutionally different products can be prepared from two types of components where each of them contains 100 different educts, whereas $(100)^2 = 100\,000\,000$ different U-4CR products can be prepared from 100 educts of its four different types.

THE STEREOSELECTIVE U-4CR

After four decades of systematic research, it became ultimately possible to form chiral α-aminoacid derivatives by the stereoselective U-4CR with 1-amino-5-thioxylose as its chiral amine component **1**, and the assistant group R^1 of their products can selectively be removed [37, 38].

$$R^1 — NH_2$$

1

* Given sets of R and S *have the intersection* $R \cap S$ with the common elements R and S. *This means* $R \cap S = \{x \mid x \subset R \text{ and } x \subset S\}$, where as a *union* is $R \cup S = \{x \mid x \subset R \text{ or } x \subset S\}$ [30, p. 3].

Soon after the discovery of the U-4CR [17] it was realized that such reactions can be accomplished stereoselectively if suitable primary amines **1** are used [39–41], and shortly later also the auxiliary group could be removed [42]. In their *Peptide Synthesis* volume of 1966 Bodanszky and Ondetti [43, p. 129] already mentioned the potential advantages of preparing α-aminoacid derivatives by the U-4CR instead of the usual multistep synthesis of peptides.

Since 1969 efficient methods of preparing chiral α-ferrocenyl-alkylamines have been introduced [44–48] and it has become possible to accomplish their stereoselective U-4CRs so that the α-ferrocenyl-alkyl groups of the products can be cleaved off and the chiral α-ferrocenyl-alkylamines can be simultaneously resynthesized. Despite its conceptual advantages this methodology was given up because the stereoselectivity and the yields of its products, including the chiral α-ferrocenyl-alkylamines, could not be achieved sufficiently well [48].

In 1988 Kunz and Pfrengle [49, 50] introduced the preparation of α-aminoacid derivatives by the U-4CR in excellent stereoselectivity and in high yields, using the chiral 2,3,4,6-tetra-O-pivaloyl-ß-D-galactopyranosylamine in the presence of $ZnCl_2$-etherate as its catalyst. One of the disadvantages of such U-4CRs is that only formic acid can be used there as the acid component. They found that the carbohydrate group of the U-4CR products of 1-amino-2,3,4,6-tetra-O-pivaloyl-ß-D-galactopyranose and related compounds can only be replaced if their products are heated in half concentrated methanolic hydrochloric acid. Then also the amide bonds are cleaved off, and only α-aminoacids or their amide derivatives are formed.

A few years later Goebel and Ugi [51–53] formed α-aminoacid derivatives by the U-4CR with tetra-O-alkyl-1-glucopyranosylamines where any carboxylic acid components can participate. Lehnhoff et al. [54] used the U-4CR with 1-amino-2-deoxy-2-N-acetylamino-3,4,6-tri-O-acetyl-ß-D-glucopyranose, whose great variety of products could be formed stereoselectively in excellent yields. Their products could not be cleaved selectively.

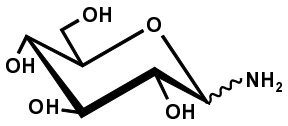
Zychlinski [55] prepared 1-amino-2-deoxy-2-acetamido-3,4,6-tri-O-acetyl-ß-D-glucopyranose by a synthesis of 11 steps. This amine component undergoes the U-4CRs very well but their products are not very stable since they are already cleaved by water.

Roß and Ugi [37] prepared 1-amino-5-deoxy-5-thio-2,3,4-tri-O-isobutanoyl-ß-D-xylopyranose from xylose via the 5-desoxy-5-thio-D-xylopyranose. The U-4CRs of this amine form the α-aminoacid derivatives stereoselectively and in excellent yields, and their products are stable, but their auxiliary 5-desoxy-5-thio-D-xylopyranose group can selectively be cleaved off by mercury(II) acetate and trifluoroacetic acid. The expected steric structure of its U-4CR was confirmed by an X-ray measurement [37].

UNPROTECTED 1-AMINO-CARBOHYDRATES AND THEIR U-4CR

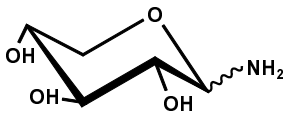
In 1985 Kochetkov and co-workers [56] introduced the preparation of the pyranosylamine **1g** from 2-acetylamino-glucose just by adding ammonia as

ammonium hydrogen carbonate in saturated aqueous solution. This method is stereospecific and gives only one anomere. The classical method of preparing unprotected 1-amino-carbohydrates using ammonia in 17% methanolic solution in the presence of ammonium carbonate is not so stereospecific as the Kochetkov synthesis [57]. Unprotected pyranosylamines **1a**–**h** (Scheme 1) are chiral amines



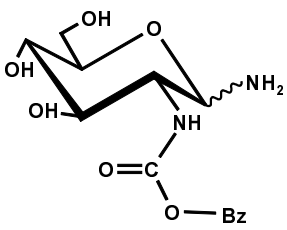
1a (α : β = 1:4.4)

61.8 %



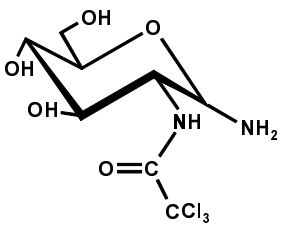
1b (α : β = 1:9.4)

96 %



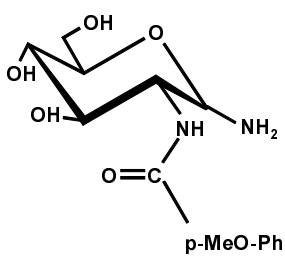
1c (α : β = 2.1:1)

87.6 %



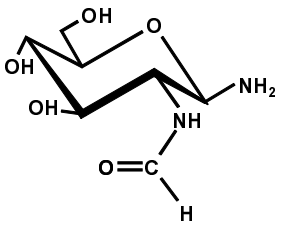
1d (α)

44.3 %



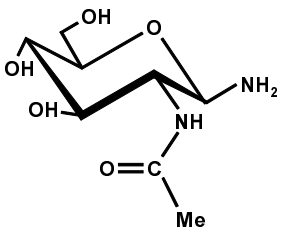
1e (α)

81.8 %



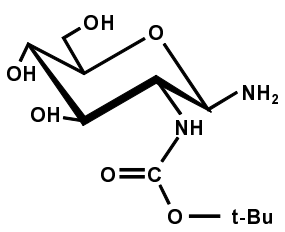
1f (ß)

72.8 %



1g (ß)

68.6 %



1h (ß)

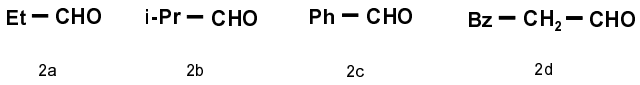
93.1 %

Scheme 1

which have in some cases an acylamino group in position 2. These amines were prepared by Kochetkov's optimal method.

D-glucopyranosylamine **1b**, 2-deoxy-2-formylamino-glucopyranosylamin **1f**, 2-deoxy-2-acetamido-ß-D-glucopyranosylamine **1g**, and 2-deoxy-2-*tert*-butoxy-carbonylamido-D-glucopyranosylamine **1h** are now easily available [58].

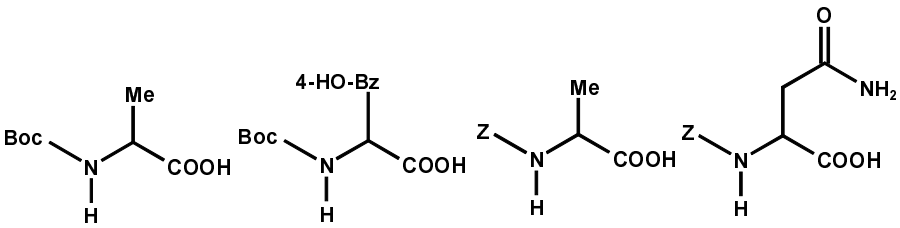
Here the pyranosylamines **1b**, **1f**–**h** are prepared by the Kochetkov method at 30 °C in 6–7 days. At 20 °C such reactions require approximately 45 days [55].



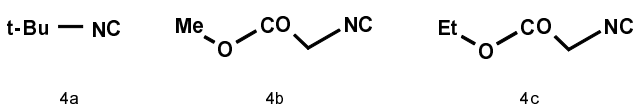
2a 2b 2c 2d

2e 2f

3a 3b 3c 3d 3e



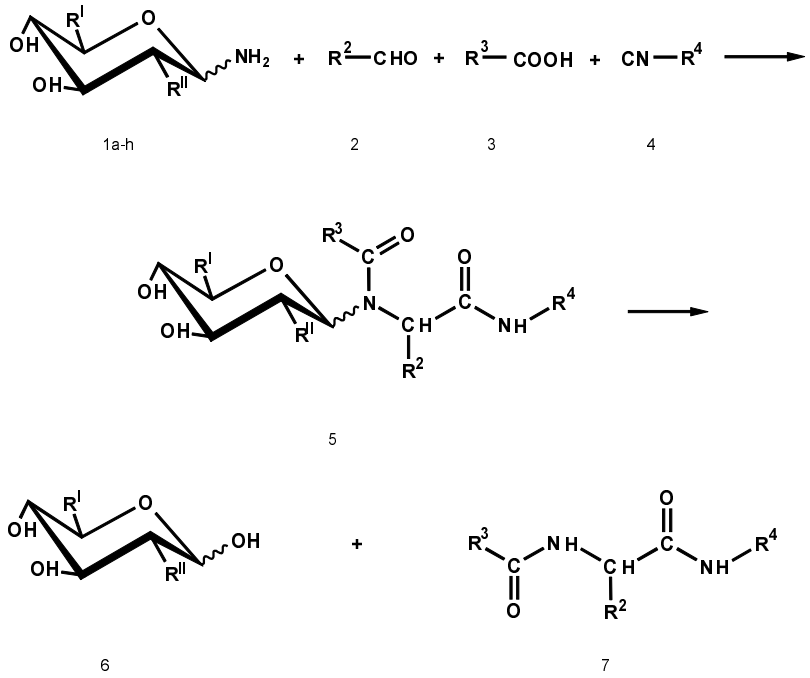
3f 3g 3h 3i



4a 4b 4c

Scheme 2

In the presence of dehydrating reagents such as a molecular sieve or magnesium sulphate, the 1-amino-carbohydrates **1a**–**h** were here precondensed with the aldehydes **2a**–**f** into their Schiff bases. Subsequently these were reacted by U-4CRs with acid components **3a**–**i** and the isocyanides **4a**–**c** at – 42 °C to + 20 °C in methanol and in some cases $ZnCl_2$-etherate was used as a catalyst (Scheme 2).



Scheme 3

The variability of forming the products **5a**–ff by the U-4CR, partly in the presence of zinc chloride as a catalyst, are demonstrated here (Table 1). However, also several other catalysts have even more positive influences on the U-4CR. Their 0.1 and 1.0 equivalents of zinc chloride (electronic configuration of $3d^{10}4s^2$), zirconium chloride ($4d^25s^2$ configuration), and cerium chloride ($4f^25d^06s^2$ configuration) were compared as their stereoselective catalysts. At lower concentrations all of these catalysts form high yields of pure products, whereas in the presence of equivalent amounts of these catalysts, low yields of less pure products result (Table 2).

Table 1. The formation of the products **5** by stereoselective U-4CR of chiral primary amines **1**, aldehydes **2**, carboxylic acids **3**, and isocyanides **4**

Products **5a**–ff	Amines **1a–h**	Aldehydes **2a–f**	Acids **3a–i**	Isocyanides **4a–c**	Catalyst $ZnCl_2$ eq.	Temperature, °C	Yield, %	d.e., %
a	a	b	b	a	0.1	+20	50	97
b	a	e	d	a	–	–32	91	63
c	a	b	d	a	–	–32	72	48
d	b	b	b	a	0.1	+20	64	34
e	b	e	b	c	–	–35	59	59
f	c	b	b	a	1.1	+20	47	–
g	c	a	h	a	–	–35	88	40
h	c	e	f	a	–	–35	87	50
I	c	d	f	a	–	+20	30	80
j	d	b	b	c	0.3	+20	80	–
k	d	e	b	a	–	–35	89	–
l	d	e	d	a	1.1	+20	90	–
m	d	b	d	a	–	–38	89	–
n	e	b	b	a	0.1	+20	45	86
o	e	c	h	a	–	–38	98	85
p	e	d	f	a	–	–38	77	60
q	f	b	a	a	1.1	–32	50	76
r	f	b	b	a	1.1	–32	32	89
s	f	e	d	b	–	–38	48	74
t	f	e	b	a	0.1	–38	78	0.62
u	f	f	i	a	–	–38	34	4.5
v	g	b	a	a	1.1	+20	73	82
w	g	e	a	a	1.1	+20	90[b]	77
x	g	d	b	a	1.1	–32	31	92
y	g	b	g	a	1.1	–35	86	90
z	g	e	b	a	1.1	–42	65	86
aa	g	e	c	a	1.1	–42	81	76
bb	g	b	b	a	0.1	–35	90	95
cc	g	d	h	b	–	–38	95	99
dd	g	d	f	a	–	–38	46	59
cc	g	e	f	b	–	–38	92	51
dd	g	f	i	a	0.3	–35	30	52
ee	h	e	d	a	1.0	–32	50	62
ff	h	a	h	a	–	–32	15	5.2

– No catalyst.

Table 2. The formation of the product **5bb** by the U-4CR without and with various catalysts

Catalyst	Yield, %	d.e., %
–	96	93
0.1 eq. $ZnCl_2$–OEt_2	99	95
1.0 eq. $ZnCl_2$–OEt_2	95	83
0.1 eq. $CeCl_3$–$7H_2O$	99	99
1.0 eq. $CeCl_3$–$7H_2O$	29	99
0.1 eq. $ZrCl_4$	99	80
1.9 eq. $ZrCl_4$	63	66

Not only α-aminoacid derivatives can be prepared stereoselectively by U-4CR syntheses but also some other products can be formed by stereoselective U-4CRs. Recently a particularly interesting one-pot synthesis of thiazole derivatives was accomplished from 1-amino-5-deoxy-5-thio-2,3,4-tri-O-isobutanoyl-ß-D-xylopyranose, an aldehyde of carboxylic acid and 2-isocyano-3-dimethylamino acrylic acid methylester as the educts [59, 60].

THE REMOVAL OF THE CARBOHYDRATE GROUPS OF THE U-4CR PRODUCTS

A variety of acidic reagents were used in order to stereoselectively cleave the products **5a**–ff of the U-4CR into **6** and **7**. The cleavage could be accomplished moderately well. It was assumed that the most efficient cleavages could be achieved if the U-4CR products contained 2-acylamino-carbohydrate groups, depending on the types of acyl groups. The U-4CR product of the amine component **1e** could thus be cleaved particularly well. Among a great variety of conditions, the treatment of the U-4CR products with 1m HCl in methanol at 40 °C for 19 h could be successfully used. There up to 30% yields of product **6** could be achieved, and in the case of **5n** the cleavage could form its α-aminoacid derivative in a yield of 46% [58].

EXPERIMENTS [58]

Pyranosylamines 1a, 1d, 1f–h

The pyranosylamines **1a**, **1d**, and **1f**–**h** were prepared analogously to the Kochetkov method [56] at 30 °C in 6–7 days. The carbohydrates (10 mmol) were dissolved in saturated aqueous solution of NH_4HCO_3. After 6 days the reaction mixture was diluted with equal volumes of water, and NH_4HCO_3 was removed as NH_3 and CO_2 by concentration in vacuo at bath temperature 27–30 °C to the original volume. This procedure was repeated 6–7 times till pH = 8.

The isolation of the glycosylamines proceeded with Amberlyst 15(H^+). After elution of the impurities with water and aqueous methanol, the pure glycosylamines were eluted with methanolic ammonia (0.5 M). At 20 °C such reactions require approximately 45 days.

Pyranosylamines 1b, 1c, 1e

The pyranosylamines **1b**, **1c**, and **1e** were prepared using ammonia as 17% methanolic solution in the presence of ammonium carbonate [55]. Here 10 mmol of carbohydrate and 0.72 g of ammonium carbonate were dissolved in 60 mL of methanol with 17% ammonia. After 3 days at room temperature, 60 mL of methanol was added four times, and each time the product solution was evaporated to 15 mL, the last time to dryness. The residue was dissolved in a small volume of methanol containing ammonia (17%) and $(NH_4)_2CO_3$ (1%) and stored at 4 °C. Next day the precipitate was filtered off.

The structures of the products were usually determined by ^{1}H-NMR, ^{13}C-NCR, and HPTC-MS measurements.

α-Aminoacid derivatives 5a–ff

In this experiment 10 mmol of pyranosylamines **1a**–**h**, 10 mmol of an aldehyde **2a**–**f**, and 5 g of molecular sieve (4 Å) were stirred in 90 mL of methanol at 20 °C till the formation of the imine was complete (DC control). At the desired reaction temperature 10.4 mmol of the carboxylic acid **3a**–**i** and 10.4 mmol of the isocyanide **4a**–**c** were added together with the needed amount of $ZnCl_2$-etherate as its catalyst. When the reaction was over (DC control; $EtOH/CH_2Cl_2$ 1 : 5; detection by methanol/sulphuric acid 5%), the suspension was filtered by a Celite layer and the solvent was removed in vacuo. The product was purified by a chromatographic column. The ratio of diastereomeric products was determined by NMR.

Cleavage of the U-4CR products 5 into the 5-desoxy-5-thio-D-xylopyranose 6 and the α-acylamino-acidamide 7

In 20 mL methanol with 1 M HCl 0.50 mmol of the U-4CR products **5** were treated at 40 °C for 19 h. Saturated aqueous solution of sodiumbiscarbonate was added till pH = 7.5–8 was reached. The solvents were evaporated in vacuo, and the residue was dissolved in water, from which the product **6** was extracted by dichloromethane. The solvent of this organic phase was evaporated, and the residue was purified by a chromatographic column.

PROSPECTS

Since 1995 the chemistry of the U-4CR, related reactions, and their libraries have been more often industrially used than any other chemical procedures. Nevertheless, the U-4CR and related MCRs still contain more areas of unused chemistry than most of the other fields of chemistry. Stereoselective U-4CRs have not been accomplished sufficiently often, although modern chiral pharmaceutical products have become very desirable. In the future also an increasing number of chiral products will be prepared by the U-4CR, and in this procedure particularly much progress will hopefully be made.

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α-aminohapete derivaatide stereoselektiivne 4-komponendiline ühepotisüntees lähtudes 1-aminosüsivesikutest ja isotsüaniididest

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Kogu eelneva sajandi jooksul oli isotsüaniidide keemia suhteliselt hooletusse jäetud keemia osa. Nn uus ajastu algas 1958. aastal, kui isotsüaniididest said hästi kättesaadavad ühendid. Aasta hiljem võeti kasutusele isotsüaniidide nn 4-komponendiline reaktsioon (U-4CR), mis võimaldas sünteesida suurt arvu ühendeid.

U-4CR-i läbiviimiseks piisab komponentide segamisest ja reaktsioon võib kulgeda füsioloogilistes tingimustes. Alates 1995. aastast on U-4CR-i produktid leidnud laia kasutust ka tööstuslikult. Kiraalsete ühendite tekketingimusi U-4CR-i puhul uuriti mitme aastakümne jooksul, kuid alles hiljuti arendati välja meetodid, kus kasutatakse 1-aminosüsivesikuid ja vastavaid amiine. 1986. aastal leidis N. K. Kochetkov koos kaastöötajatega, et 1-aminosüsivesikuid saab valmistada süsivesikute segamisel ammooniumkarbonaadiga. Siinses artiklis on näidatud, et kiraalsete ühendite stereoselektiivne süntees on efektiivselt teostatav U-4CR-i abil.