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Repetitive Ugi reactions

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Abstract—A variety of hydantoinimide and tetrazole derivatives was prepared by combining two different Ugi reactions (U-4CRs) in solid and liquid phases.

For a whole century, the chemistry of the isocyanides was a rather empty part of chemistry. Only 12 isocyanides were known and their chemistry was only moderately developed. In 1958, a new era of isocyanide chemistry began when the isocyanides became generally well available, and one year later the extremely variable four component reaction of the amines, carbonyl compounds, acid components and isocyanides was introduced.[1] Since 1962 various authors began to quote this reaction as the Ugi reaction (U-4CR).[2] In the 1971 published Isonitrile Chemistry volume[1] 325 isocyanides were described, the U-4CR had become a profound progress in chemistry.

Until the isolation of stable carbenes[3] the isocyanides were the only stable chemical compounds with a divalent carbon atom C^{II}. Their chemistry differs totally from the rest of organic chemistry. All chemical reactions of their functional group correspond to transitions of divalent carbon C^{II} to the tetravalent carbon C^{IV}. In the usual organic chemistry most reactions are conversions of one or two starting materials into their products, and the classical multicomponent reactions (MCRs) correspond to a minor part of chemistry, whereas in the chemistry of the isocyanides, their MCRs are nowadays far more often used than the reactions of two starting materials. Till recently, the isocyanides were only moderately used[2], but nowadays the chemical industry is very active in the chemistry of the U-4CRs and related reactions.[4]

The library chemistry became active in 1982 when Furka[5] introduced the peptide libraries which are formed by the multistep solid phase method of Merrifield[6], and in the following years also other solid phase libraries were introduced.[7] In 1995, the libraries of U-4CR products which were known since 1959[1,8] were industrially introduced by Weber et al.[9] and Armstrong et al.,[10] and since then this chemistry is one of the most often applied methodologies of searching for new suitable chemical products.[4]

Many types of the U-4CR and its combinations with further reactions have been developed, but till now no compounds have been formed by sequences of two different types of U-4CRs, the structures of which are extremely variable. Here we investigated the formation of products by two U-4CRs and compared these reactions in solid and liquid phases. At first α-aminoacid derivatives are formed by U-4CRs, and subsequently the second U-4CRs are carried out with trimethylsillylazide or cyanic acid as the acid components so that tetrazoles or hydantoinimides are formed. Tetrazoles[1] and hydantoinimides[11] have interesting potential pharmaceutical properties. The β-lactam antibiotic Cefamandol[12] contains a tetrazole group whereas some hydantoin derivatives have antineoplastic properties and are used as immunemodulators.[13,14]

In the first solid-phase U-4CR the polystyrene AM RAM or the TentaGel S Ram with a primary amino component reacted with the usual aldehydes and isocyanides. The Fmoc-glycine was used as the acid component. After the reaction had been finished the Fmoc-group was removed from the product in the presence of piperidine/DMF. The resulting product with its active amino group subsequently reacted with further aldehydes, 'acid components' like trimethylsilylazide or cyanic acid and isocyanides. Subsequently the solid-phase product was treated with TFA/DCM, and the hydantoin derivatives **2a**–**2d** and the tetrazole derivatives **3a** and **3b** resulted (Table 1).

Compared with former investigations[12] of single U-4CRs, the hydantoinimide derivatives could also be prepared when aromatic aldehydes are used in the second U-4CR. However, the products **2b**–**2d** had only purities of 20–40%. On the other hand, the tetrazole derivative **3a** with benzaldehyde as the aldehyde component of the subsequent

Keywords: Ugi reaction; hydantoinimide and tetrazole derivatives; solid phase and liquid phase syntheses.

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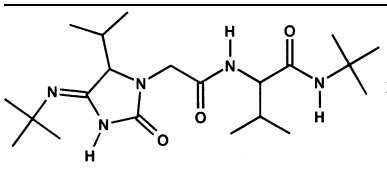
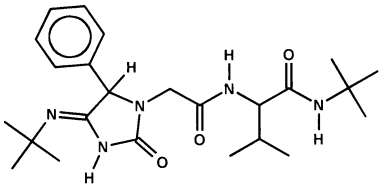
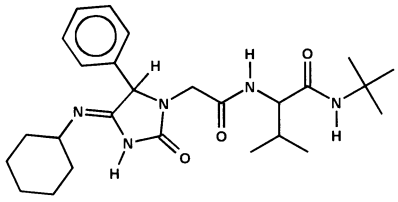
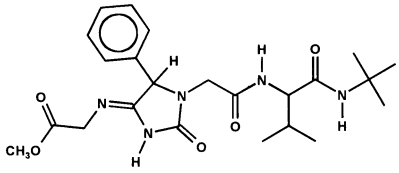
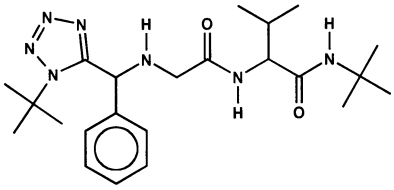
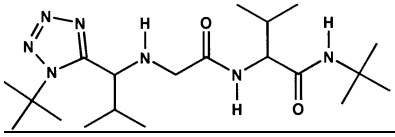
Table 1.

Product	Yield of final product (%)	Purity of final product (%)	*m/z*	
			Expected	Found
 **2a**	35[a]	72[a]	409.6	409.1
 **2b**	49[a] 65[b]	25[a] 18[b]	443.6	443.1
 **2c**	44[a] 48[b]	25[a] 15[b]	469.6	469.2
 **2d**	43[a]	38[a]	459.5	459.2
 **3a**	83[a]	88[a]	443.6	443.0
 **3b**	85[a]	73[a]	409.6	409.1

The purity was analysed by HPLC at $\lambda=254$ nm.
[a] Synthesis on polystyrene AM RAM (0.6 and 0.79 mmol/g); these swell only in nonpolar solvents.
[b] Synthesis on TentaGel (0.25 mmol/g); this resin swells in polar and nonpolar solvents.

reaction could be obtained in a purity of 88%. It is not yet clear why hydantoinimide derivatives can only be obtained in low purities when aromatic aldehydes are used.

The solid-phase syntheses of products by sequences of two U-4CRs were also compared with similar U-4CRs in liquid-phases. The latter procedures formed products in higher yields than by the comparable solid-phase syntheses (Fig. 1).

The primary U-4CRs of Fmoc-glycine in liquid phases were compared with similar solid-phase reactions, and it was found that such liquid-phase U-4CRs require less preparative work and they give usually higher yields. However, in liquid phase the starting materials have to be weighed exactly so that the products are formed in maximal yields and purity. The product **5** was not yet used as a component of a second U-4CR.

It was demonstrated that the 'repetitive U-4CR' can easily form highly substituted linear and heterocyclic compounds that could otherwise only be produced by sequences of many preparative steps. Many other types of products can also be prepared by the U-4CR particularly by using another amine and acid components. Also stereoselective syntheses of such products can probably be performed, particularly if suitable chiral amine components are used.[13]

1. Experimental

NMR spectra: Bruker spectrometer AC 200, AC 250 and

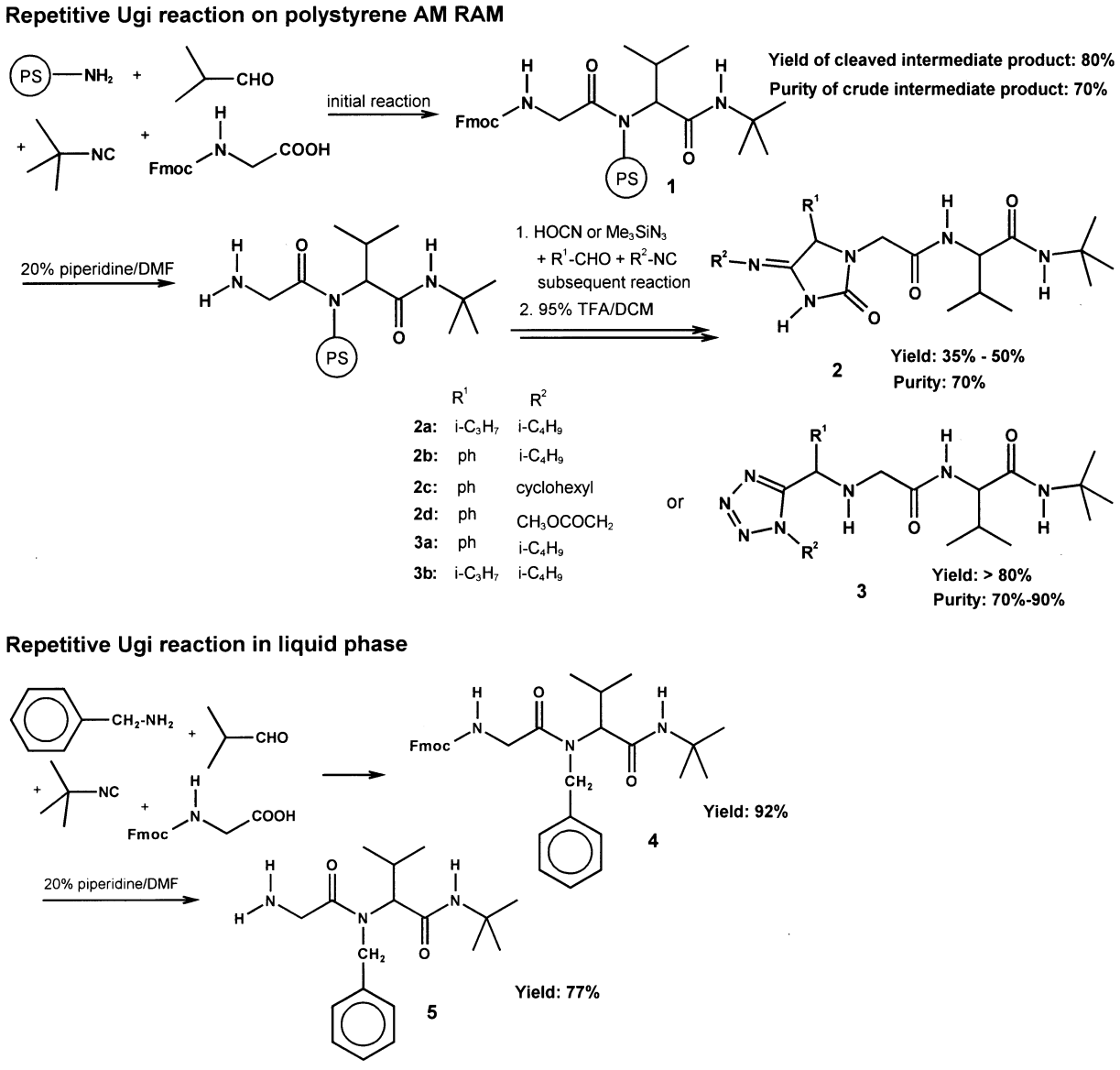


Figure 1.

AC 360. The chemical shifts are given in ppm using tetramethylsilane as internal standard. Coupling constants are listed in Hertz. Analytical HPLC measurements were carried out under reversed-phase conditions by C18-tubes with elution of 10–90% MeCN/H_2O.The detection of the molecular mass was accomplished with an electron spray-(ESI) spectrometer with a parallel coupled UV/vis detector.

The polystyrene RAM (0.60 and 0.79 mmol/g) was swollen by unpolar solvents, and the TentaGel S Ram (0.25 mmol/g) was also swollen by polar solvents. The resins and chemicals are commercially available. The solid-phase reactions were carried out in 2 and 5 ml one way injection vessels, whose contents were shaken.

1.1. General synthesis of 1 (initial reaction)

The Fmoc-protected polystyrene AM RAM, respectively, the TentaGel S RAM resin is deprotected by piperidine/dimethylformamide (DMF) (v/v) for 30 min at 20°C (2×). This is filtered off and three times washed by DMF and 1-methyl-2-pyrrolidone (NMP). The aldehyde (10 equiv. of 1 M solvent) are added to the polymer which is swollen in the presence of NMP. After 24 h the remainder of the aldehyde is removed from the solid product by washing with NMP (3×), dichloromethane (DCM) (3×) and DCM/MeOH (2/l, v/v) (3×). Subsequently the isocyanide and the *N*-Fmoc-glycine are added (10 equiv. 1 M sol.) and shaken for 24 h at 25°C. The solvent is filtered off from the insoluble product, and the latter washed by DCM/MeOH (2/1, v/v) (3×), and DCM (3×).

1.2. General procedure for the preparation of the hydantoinimides 2a–2d (subsequent reaction)

The resin **1** is deprotected by 20% piperidine/DMF (v/v) for 2×30 min and is swollen in $CHCl_3$. The aldehyde (10 equiv.) and potassium isocyanate (20 equiv.) are

added to a mixture of water and methanol (chloroform/methanol/water=5/5/1, v/v/v). Subsequently, the isocyanide (10 equiv.) and pyridine hydrochloride (20 equiv.) are added. The concentration of the mixture is 0.36 M concerning the isocyanide. The heterogenic mixture is shaken for one week. Subsequently the resin is sucked off and three times washed by chloroform/methanol/water (5/5/1, v/v/v), DCM/water (1/1, v/v) and DCM. The resin is then agitated with 95% trifluoroacetic acid/DCM for 2.5 h at room temperature, and then washed by DCM. The filtrate is evaporated and toluene is added and again evaporated. This process is repeated twice and the residue is dried in vacuo. Finally methanol is added to the crude product and 10–30 μl (c=1 mg/ml) are analysed by HPLC.

1.2.1. Compound 2a. m/z=410.1 $(m+H)^+$, 432.2 $(m+Na)^+$, 819.0 $(2m+H)^+$, 841.1 $(2m+Na)^+$; time of retention=12.6 min; solid phase: polystyrene AM RAM (yield: 35%, purity: 72%).

1.2.2. Compound 2b. m/z=244.0 $((m+2Na)/2)^{2+}$, 444.1 $(m+H)^+$, 466.3 $(m+Na)^+$, 887.0 $(2m+H)^+$, 909.1 $(2m+Na)^+$, 925.3 $(2m+K)^+$; time of retention=14.8 min; solid phase: polystyrene AM RAM, yield: 49%, purity: 25%; solid phase: TentaGel S RAM yield: 65%, purity: 18%.

1.2.3. Compound 2c. m/z=470.2 $(m+H)^+$, 492.3 $(m+Na)^+$, 961.3 $(2m+Na)^+$; time of retention=15.8 min; solid phase: polystyrene AM RAM, yield: 44%, purity: 25%; solid phase: TentaGel S RAM yield: 48%, purity: 15%.

1.2.4. Compound 2d. m/z=260.1 $((m+Na+K)/2)^{2+}$, 460.2 $(m+H)^+$, 482.2 $(m+Na)^+$, 941.0 $(2m+Na)^+$; time of retention=13.7 min; solid phase: polystyrene AM RAM, yield: 43%, purity: 38%.

1.3. General procedure for the preparation of the tetrazoles 3a and 3b (subsequent reaction)

The resin is deprotected by piperidine/DMF (v/v) for 2×30 min and is swollen by chloroform. The aldehyde (10 equiv.) is added, and subsequently methanol (chloroform/methanol=3/1, v/v), the isocyanide (10 equiv.) and trimethylsilyl azide (20 equiv.) are added. The concentration of the mixture is 2 M concerning the isocyanide. The heterogenic mixture is shaken for a week. The resin is sucked off and is three times washed by chloroform/methanol (3/1, v/v), chloroform, DCM, DCM/water (1/1, v/v) and DCM. The polymer carrier is removed by 95% TFA/DCM (2.5 h, 20°C) and the crude product is dried in vacuo. Methanol is added to the product and 10–30 μl (c=1 mg/ml) are analysed by HPLC.

1.3.1. Compound 3a. m/z=444.0 $(m+H)^+$, 466.1 $(m+Na)^+$, 886.9 $(2m+H)^+$, 909.0 $(2m+Na)^+$; time of retention=15.9 and 16.4 min (diastereomeres); solid phase: polystyrene AM RAM, yield: 83%, purity: 88%.

1.3.2. Compound 3b. m/z=410.1 $(m+H)^+$, 432.2 $(m+Na)^+$, 819.3 $(2m+H)^+$, 841.1 $(2m+Na)^+$; time of retention=13.6, 15.5 und 15.9 min (diastereomeres); solid phase: polystyrene AM RAM, yield: 85%, purity: 73%.

1.4. Synthesis of *N*-Fmoc-Glycyl-*N*-benzylvalyl-*tert*-butylamide (4) in liquid phase

Benzylamine (10 mmol) and isobutyraldehyde (10 mmol) are dissolved in 10 ml abs. ethanol. One gram of $MgSO_4$ is added and the mixture is stirred for three hours at 25°C. After filtration *N*-Fmoc-Glycine (10 mmol) and *tert*-butylisocyanide (10 mmol) are added and the mixture is stirred for 24 h at 25°C. The solvent is removed and the product is dried in vacuo (yield: 92%).

1.4.1. Compound 4. ^{1}H NMR ($CDCl_3$, 360.13 MHz): δ= 7.67–7.08 (m, 13H), 6.26 (s, 1H), 4.81 (d, 1H, ^3J=7.5 Hz), 4.27–3.59 (m, 8H), 2.31 (m, 1H), 1.20 (s, 9H), 0.88/0.76 (dd, 2×3H, ^3J=6.2 Hz, ^3J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ=170.2, 168.6, 156.1, 143.8, 141.2, 128.7–119.9, 67.0, 58.1, 56.8, 51.4, 47.0, 43.4, 28.4, 27.5, 19.4/18.8; HPLC-MS (in MeOH): m/z=542.0 $(m+H)^+$, 564.3 $(m+Na)^+$, 1082.8 $(2m+H)^+$, 1106.0 $(2m+Na)^+$; time of retention=21.2 min.

1.5. Synthesis of *N*-Glycyl-*N*-benzylvalyl-*tert*-butylamide (5) in liquid phase

3.7 mmol **4** are dissolved in 10 ml piperidine and stirred for 1.5 h at 25°C. Subsequently the mixture is poured into 200 ml of cold water and the insoluble piperidine–dibenzofulvene-adduct is filtered off. The solvent is removed at reduced pressure and the crude product is purified by silica gel (solvent: DCM/MeOH=95/5, R_f=0.4) (yield: 77%).

1.5.1. Compound 5. ^{1}H NMR (MeOD, 250.13 MHz): δ=7.34–7.23 (m, 5H), 4.78 (d, 1H, ^3J=5.2 Hz), 4.69 (s, 2H,), 4.55 (d, 2H, ^3J=5.3 Hz), 3.86 (d, 1H, ^3J=7.8 Hz), 2.42–2.30 (m, 1H), 1.30 (s, 9H), 1.0/0.93 (dd, 2×3H, ^3J=6.4 Hz, ^3J=6.7 Hz); ^{13}C NMR (MeOD, 62.90 MHz): δ=174.2, 171.3, 139.4, 129.9, 128.6, 127.4, 57.9, 66.2, 52.6, 44.4, 29.7, 29.0, 19.9, 19.4; HPLC-MS (in MeOH): m/z=320.0 $(m+H)^+$, 342.2 $(m+Na)^+$, 677.3 $(2m+K)^+$; time of retention=11.5 min.

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