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Multi-Component Reactions (MCR). VIII [1]

Synthesis of Aziridine Compounds *via* Ugi-Reaction

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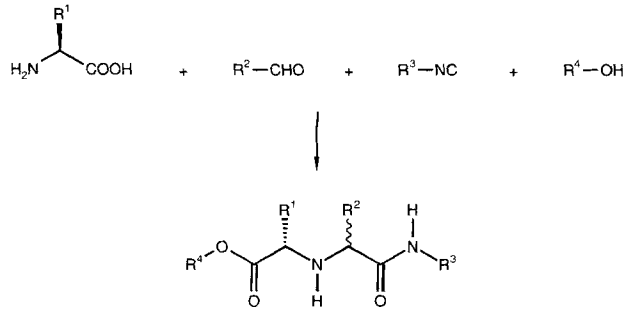
Dedicated to Prof. George Olah on the Occasion of his 70th Birthday

Multicomponent reactions (MCRs) are defined as reactions of three or more different starting materials. Their products contain at least one part of each educt [2–4].The greatest variation of products can be achieved by MCRs, whose starting materials and intermediates equilibrate, while the final step is *de facto* irreversible. This is a characteristic feature of MCRs based on isocyanides, whose first one was developed by Passerini [5], especially of the well-known Ugi-Reaction (U-4CR) [6, 7].

Today MCRs are widely used in organic syntheses [8]. They gained industrial interest as sources of pharmaceutically active compounds as they are well suited for combinatorial chemistry [9–12]. Especially isocyanide MCRs have been of increasing interest both for the solid and for the liquid phase preparation of small pseudo-peptidic compounds. As a one-pot reaction, the U-4CR is a simple and fast access to a wide variety of products which often would require several steps being synthesized by conventional two component reactions [13].

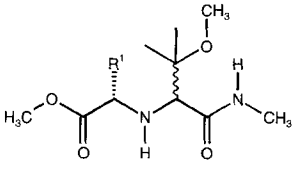
One of the recently discovered variations of the U-4CR employs a chiral β-amino acid as a starting material instead of an amine and a carboxylic acid [14]. Together with an aldehyde, an isocyanide and a nucleophile, usually an alcohol also used as a solvent, they form 1,1'-iminodicarboxylic acid derivatives **1** in nearly quantitative yields and usually high diastereomeric excesses. 1,1'-Iminodicarboxylic acids are a group of natural substances with an astonishing variety of functions and sources [15–17]. Due to its high yields and its remarkable diastereomeric excesses the so-called five-center-four-component reaction (U-5C-4CR) is a very promising access to this group of substances, especially when combined with the recently investigated methods of amide-cleavage [18].



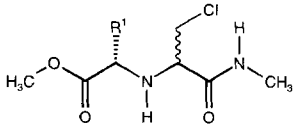
1

It has been shown that functional groups, such as the oxygen of carboxylic groups on the side chain of amino acids, may act as nucleophiles to close heterocycles or also as starting materials for subsequent MCRs in so-called tandem reactions [19]. Another way to perform secondary reactions is the use of aldehydes with reactive side chains or special isocyanide components.

A very interesting access to chiral aziridines [20] *via* β-chloroamines requires the introduction of halogen functions into the products of the U-5C-4CR by using chlorinated aldehydes [19]. While α-chloroisobutyric aldehyde quantitatively yields methyl ethers **2**, chloroacetaldehyde is an ideal compound to synthesize β-chloro 1,1'-iminodicarboxylic acid derivatives **3**.



2

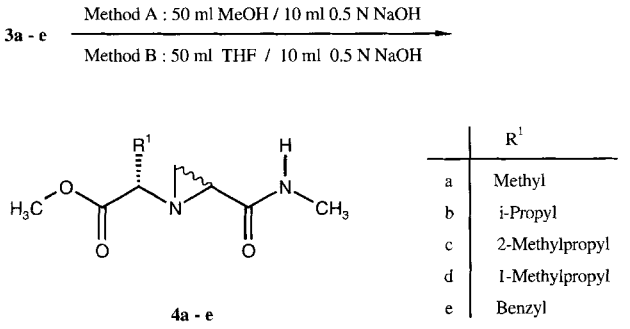


3

Yields of the first published chlorinated products of the U-5C-4CR [19] were lower than those usually found in the U-5C-4CR [21]. By using pure, distilled chloroacetaldehyde instead of its aqueous solution, yields up to 90% can be achieved.

L-Alanine, L-valine, L-leucine, L-isoleucine and L-phenylalanine as amino acid components were treated with methyl isocyanide and chloroacetaldehyde. Methanol was employed as the solvent. After this first reaction step the crude products were purified by removing residual amounts of amino acids with water. There are no other by-products. Although they are stable for several days, the chlorinated U-

5C-4CR bases should be submitted to subsequent reactions as soon as possible to avoid polymerisation. Aziridines **4a–e** can be synthesized from the crude product in a one-pot reaction either without removing methanol (method A) or by changing the solvent from methanol to tetrahydrofuran to avoid by-products caused by the nucleophilicity of methanol (method B).



	R^1
a	Methyl
b	i-Propyl
c	2-Methylpropyl
d	1-Methylpropyl
e	Benzyl

According to classical aziridine syntheses [22, 23] the cyclisation easily proceeds by adding equimolar or excess amounts of aqueous NaOH.

Method B is suitable for all the investigated U-5C-4CR β-chloroamines with exception of the L-alanine and the L-leucine compounds **3a** and **3c**. The aziridine **4a** decomposes, **4c** is accompanied by unacceptable amounts of by-products. The best results are achieved with L-valine and L-isoleucine. Both methods A and B yield aziridines **4b** and **4d** in remarkable purity.

Tab. 1 Overall yields and diastereomeric excesses of aziridines **4a–e**

Amino Acid	Yield (%) method A	Yield (%) method B	*d.e.*(%)	Aziridines
L-Ala	30	0	48	**4a**
L-Val	65	47	47	**4b**
L-Leu	49	≈ 30	49	**4c**
L-Ile	44	46	57	**4d**
L-Phe	44	41	–	**4e**

Although no X-ray structure data are yet available, the absolute configuration of the new asymmetric centre of the main diastereomer is assumed to be the same as that of U-5C-4CR products formed from aliphatic aldehydes [21, 24].

The diastereomeric excesses and, due to ester cleavage, the overall yields are lower than those observed in conventional U-5C-4CR's with aliphatic aldehydes [21].

Experimental

NMR spectra were recorded on a Bruker spectrometer AM 360 with TMS as internal standard. The chemical shifts are reported in ppm downfield from TMS. The different carbon bonding states (C, CH, CH_2 or CH_3) were assigned by ^{13}C to ^1H polarisation transfer (DEPT). Elemental analyses were performed at the microchemical laboratory of our institute.

The acquisition of GC/MS data was performed on a Varian MATCH-5 apparatus coupled to a GC Carlo Erba 4160 column. Electronic ionisation (EI; ionisation potential of 70 eV) was used. Medium pressure column chromatography (0.9–2.0 bar) was conducted on silica gel (15–40 µm, Merck) and neutral Al_2O_3 (Activity I, Merck). All commercial reagents were purchased from Aldrich, Merck and Fluka. All solvents were dried and stored under inert gas. Diastereomeric excesses were calculated with integrals of NMR spectra and GC/MS plots.

Synthesis of Aziridine Compounds *via* Ugi-Reaction

5 mmol of amino acid are suspended in 50 ml methanol and 5 mmol chloroacetaldehyde and 5 mmol methyl isocyanide are added at room temperature. The end of the reaction (after approx. 16 h, clear yellow solution) and the purity of the product are determined by thin-layer chromatography (coloured with a solution of 4,4'-tetramethyldiaminodiphenylmethane [25]), then either 10 ml of 0.5N NaOH are directly added (method A) or methanol is removed and the same volume of tetrahydrofuran is added (method B). The mixture is refluxed for 2 h. The progress of the reaction is controlled by thin-layer chromatography. After completion of the reaction the solvents are removed *in vacuo*. The oily residue is dissolved in CH_2Cl_2 and washed with small amounts of water until the water phase remains colourless. NMR and GC spectra only show small amounts of by-products. Diastereomers are separated by column chromatography. The analytical data are only given for the main diastereomer.

1-(1-(S) Methoxycarbonyl)ethyl-2-N-methyl carbamoyl aziridine (**4a**)

Yield 0.29 g = 30% (A); light yellow oil. Diastereomeric excess: 48%. – ^1H NMR (360 MHz, $CDCl_3$): δ/ppm = 1.40 (d, 3H, $\underline{CH_3}$–CH, ^3J = 7.1 Hz); 1.69 (d, 1H, N–$\underline{CH_2}$–CH, ^3J_a = 7.1 Hz); 1.99 (d, 1H, N–$\underline{CH_2}$–CH, ^3J_b = 3.1 Hz); 2.26 (dd, 1H, N–CH_2–$\underline{CH}$, ^3J_a = 7.1 Hz, ^3J_b = 3.1 Hz); 2.40 (q, 1H, CH_3–$\underline{CH}$, ^3J = 7.1 Hz); 2.79 (d, 3H, NH–$\underline{CH_3}$, ^3J = 5.3 Hz); 3.74 (s, 3H, O–$\underline{CH_3}$). – ^{13}C NMR (90.6 MHz, $CDCl_3$) : δ/ppm = 18.3 ($\underline{CH_3}$–CH); 25.6 ($\underline{CH_3}$–NH); 32.7 (N–$\underline{CH_2}$–CH); 39.9 (N–CH_2–$\underline{CH}$); 52.1 (O–$\underline{CH_3}$); 65.3 (N–$\underline{CH}$–CO); 171.6 ($\underline{CO}$–NH–CH_3); 173.0 ($\underline{CO}$–O–CH_3). – GC-MS (EI, 70 eV): *m/z* (%): 186 (4, M^+), 127 (40, M^+– CO–O–CH_3).

$C_8H_{14}N_2O_3$ (186.21) calcd.: C 51.60 H 7.58 N 15.04
found: C 51.43 H 7.50 N 15.24.

1-(1-(S) Methoxycarbonyl-2-methyl)propyl-2-N-methyl carbamoyl aziridine (**4b**)

Yield 0.70 g = 65% (A); 0.5 g = 47% (B); light yellow oil. Diastereomeric excess : 47%. – ^1H NMR (360 MHz, $CDCl_3$): δ/ppm= 1.02 (d, 3H, ($\underline{CH_3}$)$_2$–CH, ^3J = 6.6 Hz); 1.05 (d, 3H, ($\underline{CH_3}$)$_2$–CH, ^3J = 6.6 Hz); 1.75 (d, 1H, N–$\underline{CH_2}$–CH, ^3J_a = 7.1 Hz); 2.05 (d, 1H, N–$\underline{CH_2}$–CH, ^3J_b = 2.6 Hz); 2.11 (dd, 1H, N–CH_2–$\underline{CH}$, ^3J_a = 7.1 Hz, ^3J_b = 3.1 Hz); 2.10 – 2.25 (m, (CH_3)$_2$–$\underline{CH}$); 2.23 (d, 1H, N–$\underline{CH}$–CO, ^3J = 5.3 Hz); 2.80 (d, 3H, NH–$\underline{CH_3}$, ^3J = 5.3 Hz); 3.72 (s, 3H, O–$\underline{CH_3}$). – ^{13}C NMR (90.6 MHz, $CDCl_3$): δ/ppm = 18.7 (($\underline{CH_3}$)$_2$–CH); 19.1 (($\underline{CH_3}$)$_2$–CH); 25.5 ($\underline{CH_3}$–NH); 31.9 ((CH_3)$_2$–$\underline{CH}$); 35.4 (N–

$\underline{C}H_2-CH$); 37.3 (N-$CH_2-\underline{C}H$); 51.6 (O-$\underline{C}H_3$); 76.1 (N-$\underline{C}H-CO$); 170.2 ($\underline{C}O-NH-CH_3$); 172.1 ($\underline{C}O-O-CH_3$). – GC-MS (EI, 70 eV): *m/z* (%): 214 (1, M^+), 199 (1, M^+-CH_3), 155 (25, $M^+-CO-O-CH_3$), 86 (100, $CH_2-CH-CO-NH-CH_3^+$).

$C_{10}H_{18}N_2O_3$	calcd.: C 56.06	H 8.47	N 13.07
(214.26)	found: C 56.22	H 8.56	N 13.31.

1-(1-(S) Methoxycarbonyl-3-methyl)butyl-2-N-methyl carbamoyl aziridine (**4c**)

Yield 0.56 g = 49% (A); light yellow oil. Diastereomeric excess: 49%. – ^{1}H NMR (360 MHz, $CDCl_3$): δ/ppm = 0.92 (d, 3H, $(\underline{C}H_3)_2-CH$, ^3J = 6.5 Hz); 0.93 (d, 3H, $(\underline{C}H_3)_2-CH$, ^3J = 6.5 Hz); 1.59 – 1.79 (m, 3H, $(CH_3)_2-\underline{C}H-\underline{C}H_2$); 1.70 (d, 1H, N-$CH_2-CH$, ^3J_a = 7.2 Hz); 1.99 (d, 1H, N-$\underline{C}H_2-CH$, ^3J_b = 3.2 Hz); 2.20 (dd, 1H, N-$CH_2-\underline{C}H$, ^3J_a = 7.2 Hz, ^3J_b = 3.2 Hz); 2.40 (t, 1H, N-$\underline{C}H-CO$, ^3J = 6.5 Hz); 2.78 (d, 3H, NH-$\underline{C}H_3$, ^3J = 4.5 Hz); 3.72 (s, 3H, O-$\underline{C}H_3$). – ^{13}C NMR (90.6 MHz, $CDCl_3$): δ/ppm = 22.6 ($(\underline{C}H_3)_2-CH$); 22.9 ($(\underline{C}H_3)_2-CH$); 24.8 ($(CH_3)_2-\underline{C}H$); 25.7 ($\underline{C}H_3-NH$); 34.0 (N-$\underline{C}H_2-CH$); 38.7 (N-$CH_2-\underline{C}H$); 41.8 ($(CH_3)_2-CH-\underline{C}H_2$); 52.1 (O-$\underline{C}H_3$); 68.9 (N-$\underline{C}H-CO$); 170.2 ($\underline{C}O-NH-CH_3$); 173.0 ($\underline{C}O-O-CH_3$). – GC-MS (EI, 70 eV): *m/z* (%): 213 (2, M^+-CH_3), 169 (10, $M^+-CO-O-CH_3$), 86 (100, $CH_2-CH-CO-NH-CH_3^+$).

$C_{11}H_{20}N_2O_3$	calcd.: C 57.87	H 8.83	N 12.27
(228.29)	found: C 57.22	H 9.05	N 12.87.

1-(1-(S) Methoxycarbonyl-2-methyl)butyl-2-N-methyl carbamoyl aziridine (**4d**)

Yield 0.50 g = 44% (A); 0.52 g = 46% (B) light yellow oil. Diastereomeric excess: 57%. – ^{1}H NMR (360 MHz, $CDCl_3$): δ/ppm = 0.93 (t, 3H, $\underline{C}H_3-CH_2$, ^3J = 7.2 Hz); 1.02 (d, 3H, $\underline{C}H_3-CH$, ^3J = 7.1 Hz); 1.30 – 1.60 (m, 2H, $CH_3-\underline{C}H_2$); 1.74 (d, 1H, N-$\underline{C}H_2-CH$, ^3J_a = 7.2 Hz); 1.82 – 1.91 (m, 1H, $CH_3-\underline{C}H$); 2.02 (d, 1H, N-$\underline{C}H_2-CH$, ^3J_b = 3.2 Hz); 2.13 (dd, 1H, N-$CH_2-\underline{C}H$, ^3J_a = 7.2 Hz, ^3J_b = 3.2 Hz); 2.33 (d, 1H, N-$\underline{C}H-CO$, ^3J = 4.5 Hz); 2.79 (d, 3H, NH-$\underline{C}H_3$, ^3J = 5.2 Hz); 3.72 (s, 3H, O-$\underline{C}H_3$). – ^{13}C NMR (90.6 MHz, $CDCl_3$): δ/ppm= 11.3 ($\underline{C}H_3-CH_2$); 14.7 ($\underline{C}H_3-CH$); 25.4 ($\underline{C}H_3-NH$); 25.5 ($CH_3-\underline{C}H_2$); 34.5 (N-$\underline{C}H_2-CH$); 37.8 ($CH_3-\underline{C}H$); 38.3 (N-$CH_2-\underline{C}H$); 51.2 (O-$\underline{C}H_3$); 74.4 (N-$\underline{C}H-CO$); 170.0 ($\underline{C}O-NH-CH_3$); 171.7 ($\underline{C}O-O-CH_3$). – GC-MS (EI, 70 eV): *m/z* (%): 228 (1, M^+), 213 (2, M^+-CH_3), 169 (8, $M^+-CO-O-CH_3$), 86 (100, $CH_2-CH-CO-NH-CH_3^+$).

$C_{11}H_{20}N_2O_3$	calcd.: C 57.87	H 8.83	N 12.27
(228.29)	found: C 57.67	H 8.90	N 11.67.

1-(1-(S) Methoxycarbonyl-2-phenyl)ethyl-2-N-methyl carbamoyl aziridine (**4e**)

Yield 0.58 g = 44% (A); 0.54 g = 41% (B); colourless oil. Diastereomeric excess : ≈ 0; Diastereomere 1: ^{1}H NMR (360 MHz, $CDCl_3$): δ/ppm = 1.75 (d, 1H, N-$\underline{C}H_2-CH$, ^3J_a = 6.5 Hz); 1.97 (d, 1H, N-$\underline{C}H_2-CH$, ^3J_b = 3.2 Hz); 2.15 (dd, 1H, N-$CH_2-\underline{C}H$, ^3J_a = 7.1 Hz, ^3J_b = 3.2 Hz); 2.59 (t, 1H, N-$\underline{C}H-CO$, ^3J = 6.5 Hz); 2.70 (d, 3H, NH-$\underline{C}H_3$, ^3J = 5.2 Hz); 3.05 (dd, 1H, Ph-$\underline{C}H_2$, ^2J = 13.6 Hz, ^3J = 5.8 Hz); 3.16 (dd, 1H, Ph-$\underline{C}H_2$, ^2J = 13.6 Hz, ^3J = 6.5 Hz); 3.72 (s, 3H, O-$\underline{C}H_3$), 7.10 – 7.40 (m, 5H, $\underline{Ph}-CH_2$). – ^{13}C NMR (90.6 MHz, $CDCl_3$): δ/ppm = 25.4 ($\underline{C}H_3-NH$); 34.1 (N-$\underline{C}H_2-CH$); 38.4 (N-$CH_2-\underline{C}H$); 38.7 (Ph-$\underline{C}H_2$); 52.1 (O-$\underline{C}H_3$); 71.9 (N-$\underline{C}H-CO$); 126.9 – 136.9 ($\underline{Ph}-CH_2$); 170.0 ($\underline{C}O-NH-CH_3$); 171.7 ($\underline{C}O-O-CH_3$); Diastereomere 2: ^{1}H NMR (360 MHz, $CDCl_3$): δ/ppm = 1.36 (d, 1H, N-$\underline{C}H_2-CH$, ^3J_a = 7.1 Hz); 1.81 (d, 1H, N-$\underline{C}H_2-CH$, ^3J_b = 3.2 Hz); 1.92 (dd, 1H, N-$CH_2-\underline{C}H$, ^3J_a = 7.1 Hz, ^3J_b = 3.2 Hz); 2.59 (t, 1H, N-$\underline{C}H-CO$, ^3J = 6.5 Hz); 2.75 (d, 3H, NH-$\underline{C}H_3$, ^3J = 4.5 Hz); 3.05 (dd, 1H, Ph-$\underline{C}H_2$, ^2J = 13.6 Hz, ^3J = 5.8 Hz); 3.16 (dd, 1H, Ph-$\underline{C}H_2$, ^2J = 13.6 Hz, ^3J = 5.2 Hz); 3.69 (s, 3H, O-$\underline{C}H_3$), 7.10 – 7.40 (m, 5H, $\underline{Ph}-CH_2$). – ^{13}C NMR (90.6 MHz, $CDCl_3$): δ/ppm = 25.6 ($\underline{C}H_3-NH$); 34.4 (N-$\underline{C}H_2-CH$); 39.0 (N-$CH_2-\underline{C}H$); 39.4 (Ph-$\underline{C}H_2$); 52.1 (O-$\underline{C}H_3$); 72.2 (N-$\underline{C}H-CO$); 126.9 – 136.9 ($\underline{Ph}-CH_2$); 170.0 ($\underline{C}O-NH-CH_3$); 171.7 ($\underline{C}O-O-CH_3$); Identical for both diasteromeres: GC-MS (EI, 70 eV): *m/z* (%): 262 (15, M^+), 204 (15, $M^+-CO-NH-CH_3$), 203 (15, $M^+-CO-O-CH_3$), 171 (70, M^+-CH_2-Ph), 91 (100, CH_2-Ph^+).

$C_{14}H_{18}N_2O_3$	calcd.: C 64.11	H 6.92	N 10.68
(262.31)	found: C 63.67	H 7.00	N 10.45.

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