4 Ugi Four-component reactions (U-4CR) with siloxycyclopropanes

In 1959, Ugi et al. described the most frequently employed variants of the four-component condensation, the U-4CRs. It was postulated that the reaction involved a sequence of:

a) imine formation (step 1),
b) protonation of the imine by acid thus strongly increasing the electrophilicity of the C=N bond (step 2),
c) α-addition of the electrophilic iminium cation and the nucleophilic carboxylate anion to isocyanide (step 3) and
d) intramolecular acyl-transfer (step 4) (Scheme 32).[^81]

α-Acylaminoamides 36 were formed, compounds which could be involved in a variety of important biological activities.

![Scheme 32. Mechanism of U-4CR](image)

[^81]: Scheme 32. Mechanism of U-4CR
The α-adduct 76 formed in step 3 can be regarded as hetero analogue of an acid anhydride in which an exo-oxygen atom has been substituted by an N-R^4 group and thus as strong acylating agent. The closest nucleophilic atom is the nitrogen of the former amine and therefore the stable Ugi product is obtained after an intramolecular acylation and subsequent rearrangement to an amide. This type of intramolecular acylation was first described in 1910 by Mumm and was afterwards called Mumm rearrangement.[82, 83] All elementary steps of this reaction sequence are equilibria; however, the rearrangement to the stable α-acylaminoamide 36 lies exclusively on the product side. The overall driving force is the conversion of a high-energy isocyanide carbon atom into the tetravalent amide carbon atom. The reaction is versatile in the starting materials, comprising both aliphatic and aromatic compounds. The reaction is ecologically gentle, since only one molecule of water is lost in an entire process creating new four chemical bonds.

### 4.1 Ugi Five-center four-component reaction (U5-4CR)

α-Amino acids 77 may also be employed as amine component and by use of alcohol 81 as solvent the Ugi-4CR could be extended to an Ugi 5-center-4-component reaction (U5-4CR) providing functionalized α-amino diacid derivatives 82 via the iminium ion 78 and elusive cyclic intermediate O-acylamide 80. A new stereocenter is created at the initially carbonyl carbon atom of the aldehyde. Its preferred absolute configuration is induced by the chiral amino acid employed. Apart from cysteine, all known natural and many unnatural α-amino acids can undergo this reaction.[84]
Scheme 33. Mechanism of U5-4CR

The Ugi-reaction with methyl 2-siloxycyclopropanecarboxylates as masked carbonyl compounds, the α-amino acid L-phenylalanine and several isocyanides generated in moderate to good yields functionalized α-amino diacid derivatives 84 and pyrrolidinones 85, which represent interesting peptidomimetics.[2] 2-Siloxycyclopropanecarboxylates may directly be introduced as precursor compounds since under protic conditions as employed for this reaction, they undergo smooth cleavage to furnish γ-oxocarboxylates. The reaction temperature was allowed to rise from –30°C to room temperature. The solvent was evaporated and the residue was purified by column chromatography and in some cases by HPLC.[40] Primary adducts 84 undergo cyclization to pyrrolidinones 85 under the reaction conditions employed, as depicted in Scheme 34.
The concept to apply methyl 2-siloxycyclopropanecarboxylates in U5-4CR was first introduced by Zimmer et al.\textsuperscript{[40]} They reacted methyl 2-siloxycyclopropanecarboxylates 53 and 60 and three \(\alpha\)-amino acids with \textit{tert}-butylisocyanide to obtain primary Ugi adducts in moderate to good yields. They have also introduced methyl 2-methyl-2-siloxycyclopropanecarboxylate 86, which is equivalent to methyl levinulate, into this modification of Ugi reaction, but this reaction was inefficient under standard conditions and only 16\% of the corresponding adduct containing a quaternary center were isolated (Scheme 35).
Scheme 35: Results of U5-4CR performed by Zimmer et al.

For further exploration of this reaction methyl 2-siloxycyclopropanecarboxylates 53, 54 and 60 have been reacted with L-phenylalanine and five isocyanides in methanol. The results of these reactions are listed in Table 1.
Table 1. Results of the U5-4CR according to Scheme 28 (experiments: E2-E6, E8, E9, E11, E12)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R. Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>diastereomer ratio (%)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>diastereomer ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>H</td>
<td>H</td>
<td>PhCH₂</td>
<td>96</td>
<td>84a</td>
<td>32</td>
<td>82:18</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>H</td>
<td>H</td>
<td>n-Bu</td>
<td>54</td>
<td>84b</td>
<td>22</td>
<td>83:17</td>
<td>85b</td>
<td>4</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>H</td>
<td>H</td>
<td>MeO₂C-CH₂</td>
<td>118</td>
<td>84c</td>
<td>12</td>
<td>56:44</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Me</td>
<td>H</td>
<td>PhCH₂</td>
<td>24</td>
<td>84d</td>
<td>10</td>
<td>84:16</td>
<td>85d</td>
<td>13</td>
<td>53:47</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>Me</td>
<td>Me</td>
<td>PhCH₂</td>
<td>88</td>
<td>84e</td>
<td>32</td>
<td>80:20</td>
<td>85e</td>
<td>39</td>
<td>86:14</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>Me</td>
<td>Me</td>
<td>n-Bu</td>
<td>89</td>
<td>84f</td>
<td>17</td>
<td>82:18</td>
<td>85f</td>
<td>34</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>Me</td>
<td>Me</td>
<td>MeO₂C-CH₂</td>
<td>118</td>
<td>84g</td>
<td>4</td>
<td>81:19</td>
<td>85g</td>
<td>6</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>Me</td>
<td>Me</td>
<td>p-Methoxyphenyl</td>
<td>111</td>
<td>84h</td>
<td>38</td>
<td>92:8</td>
<td>85h</td>
<td>32</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>Me</td>
<td>Me</td>
<td>Cyclohexenyl</td>
<td>208</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>85i</td>
<td>27</td>
<td>&gt; 95:5</td>
</tr>
</tbody>
</table>
When reacted with benzylisocyanide and methyl cyanoacetate, siloxycyclopropane 53 afforded only \( \alpha \)-amino diacid derivatives 84a and 84c, respectively, and no cyclic compounds were isolated. On the contrary, siloxycyclopropane 54 in reaction with cyclohexenylisocyanide gave only cyclic compound 85i.

Siloxycyclopropanes 53 and 54 afforded after cleavage achiral aldehydes which reacted in the Ugi-reaction. In these examples only two diastereoisomers of the product were observed. The diastereoselectivity induced by the stereogenic center of the amino acid is moderate to good (ca. 4:1 to 12:1; in entries 2, 6, 7, 8 and 9 corresponding pyrrolidinones were obtained as a single diastereoisomers), except in entry 4 where a mixture of approximately 1:1 of diastereoisomers was obtained.

When siloxycyclopropane 60 was used, in situ generated \( \beta \)-formyl ester 61 is chiral but racemic. Compounds 84d and 85d were also isolated as mixtures of only two diastereoisomers, although four diastereoisomers could be expected in this case (entry 4).

The reaction is general for both aliphatic and aromatic isocyanides. Yields ranged between 12 and 71%. It was observed that yields depended on the nature of the aldehyde component: 3,3 dimethyl substituted 2-siloxycyclopropane gave the best yields. Among isocyanides, aromatic isocyanides (phenyl- and \( p \)-methoxyphenylisocyanide) gave better results than aliphatic isocyanides.

It can be concluded that most promising reactions were generally observed with 3,3-dimethyl-substituted siloxycyclopropane 54 and benzylisocyanide (71%, Table 1, entry 5), and \( p \)-methoxyphenylisocyanide (70%, Table 2, entry 8).

### 4.1.1 NMR and IR data of compounds 84 and 85

Characteristics in the \(^1\)H NMR spectra of phenylalanine derived primary Ugi adducts are the signals of the benzyl group of the amino acid moiety in the range of \( \delta = 2.7 \) to 3.3 ppm as multiplets, of the methyl ester in the range of \( \delta = 3.5 \) to 3.8 ppm as singlets and of amide NH in the range of \( \delta = 6.2 \) to 8.7 ppm as broad singlets.
Table 2. Characteristic $^1$H chemical shifts of primary Ugi adducts 84a-h; δ(ppm) (CDCl$_3$)

<table>
<thead>
<tr>
<th>Primary Ugi adduct</th>
<th>CH$_2$-Ph</th>
<th>amide NH</th>
</tr>
</thead>
<tbody>
<tr>
<td>84a</td>
<td>2.98-3.33</td>
<td>6.77[a]; 7.50</td>
</tr>
<tr>
<td>84b</td>
<td>2.81-3.22 / 2.91-3.08[a]</td>
<td>7.12-7.34; 6.36[a]</td>
</tr>
<tr>
<td>84c</td>
<td>2.98-3.14</td>
<td>6.69; 7.55[a]</td>
</tr>
<tr>
<td>84d</td>
<td>2.93-3.14</td>
<td>6.67[a]; 7.02</td>
</tr>
<tr>
<td>84e</td>
<td>2.70-2.89</td>
<td>6.97-7.29</td>
</tr>
<tr>
<td>84f</td>
<td>3.18-3.27</td>
<td>6.23[a]; 6.71</td>
</tr>
<tr>
<td>84g</td>
<td>2.95-3.10</td>
<td>6.60[a]; 7.39</td>
</tr>
<tr>
<td>84h</td>
<td>2.83-3.06 / 2.66-2.75[a]</td>
<td>8.17[a]; 8.86</td>
</tr>
</tbody>
</table>

[a] minor isomer

The most significant signal in the $^1$H NMR spectra of pyrrolidinones 85 is the proton at position 2 in the pyrrolidinone ring which appears at δ ≈ 3 ppm. Further characteristics are the signals of the α-proton of the amino acid moiety as a doublet of doublet with coupling constants 5 Hz to 6 Hz and 10 Hz to 11 Hz at δ = 3.9 to 4.2 ppm and the protons at position 4 in the pyrrolidinone ring, which in 3,3-disubstituted pyrrolidinone rings appear as doublets with coupling constant ≈ 17 Hz at δ = 1.9 to 2.4 ppm.

Table 3. Characteristic $^1$H chemical shifts of pyrrolidinones 85b-i; δ(ppm) and J(Hz) (CDCl$_3$)

<table>
<thead>
<tr>
<th>Pyr.</th>
<th>2-H</th>
<th>NCH</th>
<th>$^3$J</th>
<th>4-H</th>
<th>$^2$J</th>
<th>OMe</th>
<th>NH</th>
</tr>
</thead>
<tbody>
<tr>
<td>85b</td>
<td>2.97-3.08</td>
<td>3.86-3.91</td>
<td>2.15-2.46</td>
<td>3.90</td>
<td>8.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85d</td>
<td>2.89-3.15</td>
<td>3.86-3.99</td>
<td>1.82-2.62</td>
<td>3.64</td>
<td>8.02; 8.12[a]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85e</td>
<td>3.02[a]; 3.08</td>
<td>4.02</td>
<td>10.1; 6.0</td>
<td>1.97[a]; 2.28[a] / 2.00; 2.26</td>
<td>16.9[a]; 16.7</td>
<td>3.58[a]; 3.60</td>
<td>7.80</td>
</tr>
<tr>
<td>85f</td>
<td>3.12</td>
<td>4.07-4.19</td>
<td>2.06/2.32</td>
<td>16.8</td>
<td>3.82; 7.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85g</td>
<td>3.22</td>
<td>3.88-4.15</td>
<td>2.06/2.37</td>
<td>16.7</td>
<td>3.71; 3.79</td>
<td>8.08</td>
<td></td>
</tr>
<tr>
<td>85h</td>
<td>3.12</td>
<td>4.18</td>
<td>10.8; 5.5</td>
<td>2.10/2.37</td>
<td>16.8</td>
<td>3.78; 3.90</td>
<td>9.47</td>
</tr>
<tr>
<td>85i</td>
<td>3.01</td>
<td>4.11</td>
<td>10.2; 5.9</td>
<td>2.05/2.32</td>
<td>16.9</td>
<td>3.85; 8.30</td>
<td></td>
</tr>
</tbody>
</table>

[a] minor isomer

In the $^{13}$C NMR spectra, characteristic for compounds 85 are chemical shifts of C-3, which range between δ = 31.0 to 36.7 ppm, chemical shifts for α-carbon of the amino acid moiety at δ = 58.1 to 59.4 ppm and of C-2 at δ = 64.0 to 74.9 ppm.

IR spectra (KBr) of the compounds 85b - 85i show characteristic bands at 1740-1745 [ν(C=O) (ester)] and 1665-1700 cm$^{-1}$ [ν(C=O) (amide)].
4.2 Lactam formation

Primary adducts 84 could efficiently be cyclized by heating in toluene for 3 hours providing the desired pyrrolidinone derivatives 85 in good to excellent yields, as had been shown in previous work of Zimmer et al. (Scheme 36)[40]:

\[
\begin{align*}
\text{84} & \rightarrow \text{Toluene} \quad \text{Reflux / 3 h} \quad \text{85} \\
R^1 = \text{Me}; R^2 = \text{Bn} & \quad 81 \% (50:42:4:4) \\
R^1 = \text{Me}; R^2 = \text{CH}_2\text{Indolyl} & \quad 69 \% (52:42:3:3) \\
R^1 = \text{Me}; R^2 = \text{Me} & \quad 71 \% (34:22:22:22) \\
R^1 = \text{H}; R^2 = \text{Bn} & \quad 98 \% (90:10) \\
R^1 = \text{H}; R^2 = \text{Me} & \quad 86 \% (64:36) \\
R^1 = \text{H}; R^2 = \text{CHMeEt} & \quad 82 \% (79:21)
\end{align*}
\]

Scheme 36: Cyclizations of the primary Ugi adducts 84 to 85

Zimmer et al. also attempted a one-pot protocol from siloxycyclopropanes to pyrrolidinones[40] With siloxycyclopropane 60 a one-pot protocol was successfully performed and corresponding pyrrolidinone was obtained in 67% overall yield. However, it seemed that for 3,3-dimethyl-2-trimethylsiloxycyclopropane 54, which is the precursor of β-dimethyl-substituted β-formyl ester 59, the steric hinderance exhibited by the two methyl groups hamper the Ugi reaction considerably and the corresponding pyrrolidinone derivative was isolated in only 16% yield and negligible diastereoselectivity (Scheme 37).
Scheme 37: One-pot synthesis of substituted pyrrolidinones 85

Following these initial experiments the one-pot protocol was attempted with siloxycyclopropane 54, three isocyanides and L-phenylalanine and pyrrolidinones 85e, g, j were successfully obtained (Scheme 38). The crude product from U5-4CR was dissolved in p-xylene and refluxed for 3 hours. The solvent was evaporated and the residue was purified by column chromatography.[40] The overall transformation may be classified as 6-center 4-component reaction (6-C 4CR).

Scheme 38. One-pot synthesis of substituted pyrrolidinones (experiments: E7, E10, E13)

These experiments have shown that even with sterically hindered siloxycyclopropane 54 satisfactory results could be obtained in a one-pot protocol. The described one-pot protocol proved to be the more favorable method for synthesis of compound 85g compared to the previously described U5-4CR. Thus, only 10% overall yield was obtained (Table 1, entry 7).
under normal Ugi conditions, while latter experiment including refluxing in \( p \)-xylene afforded 78% of cyclic compound. The reaction involving benzylisocyanide was also slightly improved: 74% towards 71% in typical U5-4CR (Table 1, entry 5). Experiment with 1,1,3,3-tetramethylbutylisocyanide was performed only as one-pot protocol for obtaining cyclic compound \( 85j \).

Compounds \( 85e \) and \( j \) were isolated as mixtures of two diastereoisomers. The ratio of diastereoisomers for compound \( 85e \) was exactly the same as in the previous experiment, although under the rather harsh cyclization conditions isomerization at the stereogenic center \( \alpha \) to the carbonyl group might occur to some extend. This seems to happen with compound \( 84e \) which has been isolated in this experiment with a ratio of diastereoisomers of 85:15 compared to 80:20 in the previous experiment. Compound \( 85g \) was isolated as only one diastereoisomer as in the previous experiment (Table 1, entry 7). It was possible to grow suitable crystals from the major diastereoisomer of \( 85j \), which could be analyzed by an X-ray crystallography (Figure 1).
This measurement established the $R$-configuration of the major diastereoisomer at the pyrrolidine ring, which is in accordance with the configuration of a product in related examples.\cite{40,85} On this basis it could be suggested that the preferred attack of the isocyanide to the intermediate iminium ion A formed from the aldehyde and the amino acid proceeds from the front side giving a nitrilium ion B (Scheme 39). Cyclic intermediate C is formed, then ring-opened by methanol to afford the isolated product D. The front side attack is more favoured and hence the diastereoselectivity higher if substituent R$_2$ is larger.\cite{40}

**Figure 1** Structure of compound 85j determined by X-ray crystallography
Scheme 39.

From the X-ray crystallography results it was also possible to observe an intermolecular hydrogen bonding between the amide hydrogen of one molecule and the carbonyl oxygen of the other molecule of the compound 85j (Figure 2).

In the crystal two crystallographically distinct molecules are associated into chains through hydrogen bonds (N2 – H2 ⋯ O1: 0.857 and 2.052 Å) with an N ⋯ O separation of 2.899 Å.
Figure 2 – Intermolecular hydrogen bonds
4.3 Microwave assisted cyclization

The use of microwaves as an energy source for chemical reactions and processes has been extensively investigated during recent years, but the experimental details and the microwave systems used are still insufficiently described. Microwave techniques in synthetic chemistry often elicit a dramatic increase of the reaction rate and yields. There are reports which suggest that such dramatic improvements can be regarded as a consequence of increased temperatures caused by superheating or concentration effects. In microwave dielectric heating, the microwave energy is introduced into the chemical reactor remotely and direct access by the energy source to the reaction vessel is obtained. The microwave radiation passes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel itself. If the apparatus is properly designed, the temperature increase will be uniform throughout the sample, which can lead to the less by-products and/or decomposition products. In pressurized systems, it is possible to rapidly increase the temperature far above the conventional boiling point of the solvent used.

Attempts to cyclize compound 85e, used as a mixture of two diastereoisomers, by refluxing in toluene have failed and starting material was recovered in this experiments. Microwave-assisted (power of 1000 W) cyclization in ethylene glycol afforded bicyclic compound 86 as a single diastereoisomer in 37% yield after extraction and purification by column chromatography.

Scheme 40. Microwave-assisted cyclization reaction of 85e to the bicyclic compound 86 (experiment: E14)
4.4 Ester hydrolysis

In order to obtain free carboxylic acid 87, hydrolysis of pyrrolidinone 85g with 3 equivalents of LiOH in H₂O/MeOH/THF mixture was performed. The reaction mixture was stirred overnight at room temperature and after acidic workup monoacid derivative 87 was obtained in 59% yield as a mixture of two diastereoisomers in a ratio 71:29. Although starting compound 85g was used as a single diastereoisomer under the reaction conditions applied for this reaction epimerization occurred and the product was isolated as a mixture of two diastereoisomers (Scheme 41).

![Scheme 41. Base-mediated hydrolysis of 85j (experiment: E15)](image)

To obtain diacid compound 88, monoacid 87 was subjected to further hydrolysis as a mixture of diastereoisomers. After stirring with another 3 equivalents of LiOH in H₂O/MeOH/THF mixture at room temperature over 12 hours, diacid 88 was obtained in 92% yield, ratio of diastereoisomers is 84:16 (Scheme 42).
Scheme 42. Base-mediated hydrolysis of $87$ to diacid $88$ (experiment: E16)

To preserve configuration hydrolysis under acidic conditions has been attempted. Compound $85g$ as a single diastereoisomer was dissolved in diethyl ether, than 3 M HCl solution was added and the reaction mixture stirred at room temperature over night. Compound $87$ was isolated after workup in 30% yield as only one diastereoisomer. The significantly lower yield in this reaction is understandable since acid-catalyzed ester hydrolysis is an equilibrium reaction without a way of shifting the equilibrium to the right. Compound $85g$ was reisolated in 52 % yield (Scheme 43).

Scheme 43. Acid-catalyzed hydrolysis (experiment: E17)
4.5 Conclusion

In conclusion, these findings extend the previously published application of methyl 2-siloxycyclopropanecarboxylates in the Ugi 5-center 4-component reaction to new inputs. The primary products 84 are interesting because the four functional groups provide many possibilities for further transformations; compounds of this type also may possess biological activity. The cyclized products 85, which are highly functionalized pyrrolidinones and therefore interesting peptidomimetics, can be obtained either under standard conditions of U5-4CR, or, in higher yields, in a one-pot sequence which can be classified as a 6-center 4-component reaction. The compounds 85 can be further modified to yield interesting bicyclic compounds as 86 or mono- and diacid derivatives such as 87 and 88. Since precursor cyclopropanes are easily available in many structural variations, this modification of Ugi reaction should enable synthesis of highly diverse libraries of compounds 84 and 85. The diastereoselectivity of the reactions is moderate to good.