Seven-component reactions by sequential chemoselective Ugi–Mumm/Ugi–Smiles reactions†

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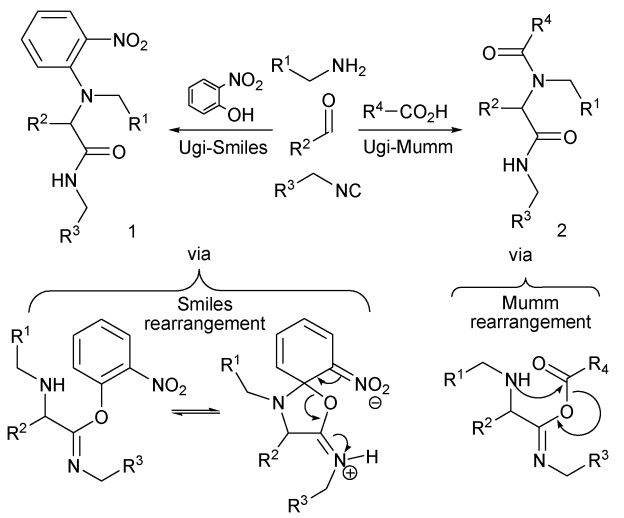
A seven-component reaction was accomplished by utilizing the different chemoselectivities of the Ugi–Mumm and the Ugi–Smiles reaction. The sequential multicomponent reactions led to highly diverse peptide and glycopeptide like structures.

Isonitrile based multicomponent reactions (IMCR's) have found numerous applications due to the high degree of product diversity which can be accomplished in a single reaction step.[1,2] In addition, the Ugi and Passerini reactions are the best known IMCR's and have attracted attention due to the possibility of tandem MCR's.[3] The inherent problem of side reactions has to be overcome. If a bifunctional, monoprotected reagent is included, repetitive Ugi reactions can be carried out, but only after an additional deprotection step.[4] The combination of the Asinger and the Ugi reaction circumvents these problems, the Asinger product functions as the imine in the subsequent Ugi reaction.[5] If the Ugi reaction is preceded by a Petasis–Mannich reaction, a seven component multicomponent reaction can be accomplished leading to peptoid/peptide substructures.[6]

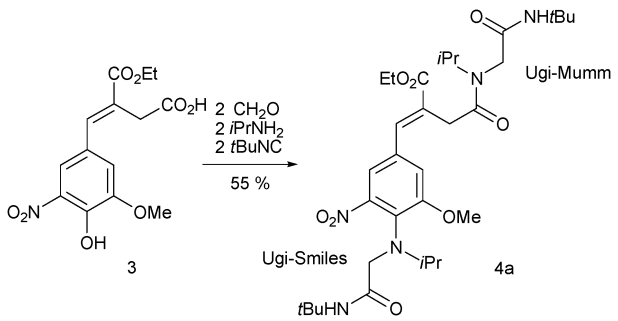
An intriguing extension of the Ugi protocol was published only recently by El Kaïm *et al.* (Scheme 1).[8] Here, the carboxylic acid was changed to an electron poor nitrophenol. The increased phenol acidity is sufficient to serve as the acidic building block. In the final, irreversible step, the Smiles rearrangement leads to the synthesis of N-arylated peptoids **1**. In further studies it could be shown that electron poor aromatic moieties *e.g.* pyridines and pyrimidines can be used, too.[8]



Scheme 1 Ugi–Mumm/Ugi–Smiles reaction.[7]

In studies using the Ugi protocol for the derivatization of the nitro caffeic acid derivative **3**[9] we became aware of competing Ugi–Mumm and Ugi–Smiles reactions (Scheme 2). Using equimolar amounts of **3** as acid component, formaldehyde, isopropyl amine and *tert*-butyl isonitrile, three products could be identified, the Ugi–Mumm, the Ugi–Smiles and the Ugi–Mumm/Ugi–Smiles product **4**. While studying this combinatorial effect further, electron poor hydroxy carboxylic acids **3** and **5–8** and two equivalents each of the other building blocks (Table 1) were used. Under these conditions (formaldehyde, isopropyl amine; *tert*-butyl isonitrile, stirring overnight at rt), the Ugi–Mumm/Ugi–Smiles product **4a** was formed in 55% yield (entry 1). Considering that eight bonds are formed, the yield for each bond forming step exceeds 90%. The benzoic acid **5** yields the products **9a–c** in 52–68% (entries 4–6), whereas the nicotinic acid **6** is incorporated in **10** in 25% (entry 7, 85% per bond formed) yield. Limitations can be observed while using fluoro-substituted benzoic acids **7** and **8**, from which only Ugi–Mumm products **12** and **13** were obtained.

The high diversity that can be generated by these tandem multicomponent reactions is exemplified by varying some components. Most notable with isobutyric aldehyde (entry 3), **4c** was formed almost quantitatively. The quantitative formation of **4c** offered the possibility to study the chemoselectivity of the two MCR's. Under controlled conditions, while adding equimolar amounts of isopropyl amine, isobutyric aldehyde and *tert*-butyl isonitrile, the distribution of



Scheme 2 Ugi–Mumm/Ugi–Smiles reaction on caffeic acid derivatives.

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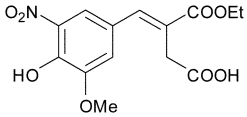
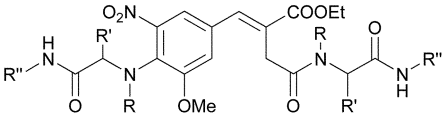
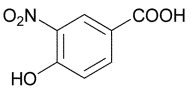
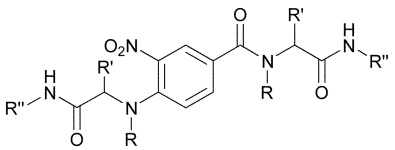
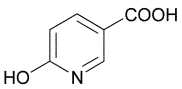
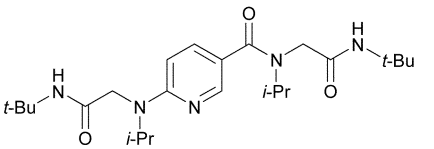
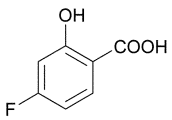
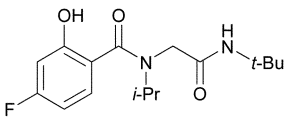
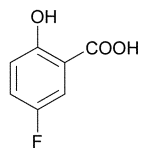
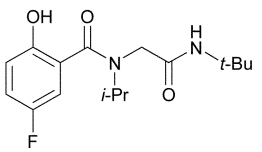
Table 1 Products by isocyanide-based multicomponent reactions

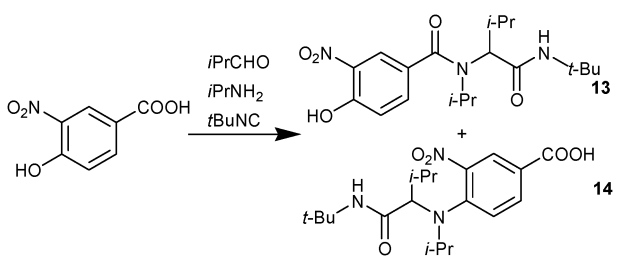
Entry	Acid	Amine/Aldehyde/ Isonitrile	Product	Yield (%)
1	 **3**	*i*PrNH$_2$/CH$_2$O/ *t*BuNC	 **4**	55
2		BnNH$_2$/CH$_2$O/ *t*BuNC		60
3		*i*PrNH$_2$/*i*PrCHO/ *t*BuNC		98[a]
			a: R=*i*-Pr; R'=H; R''=*t*-Bu b: R=Bn; R'=H; R''=*t*-Bu c: R=Bn; R'=*i*-Pr; R''=*t*-Bu	
4	 **5**	*i*PrNH$_2$/CH$_2$O/ *t*BuNC	 **9**	68
5		*i*PrNH$_2$/CH$_2$O/ *c*HexNC		58
6		BnNH$_2$/CH$_2$O/ *n*BuNC		52
			a: R=*i*-Pr; R'=H; R''=*t*-Bu b: R=*i*-Pr; R'=H; R''=Cy c: R=Bn; R'=H; R''=*n*-Bu	
7	 **6**	*i*PrNH$_2$/CH$_2$O/ *t*BuNC	 **10**	25
8	 **7**	*i*PrNH$_2$/CH$_2$O/ *t*BuNC	 **11**	43
9	 **8**	*i*PrNH$_2$/CH$_2$O/ *t*BuNC	 **12**	72

[a] Mixture of stereoisomers.

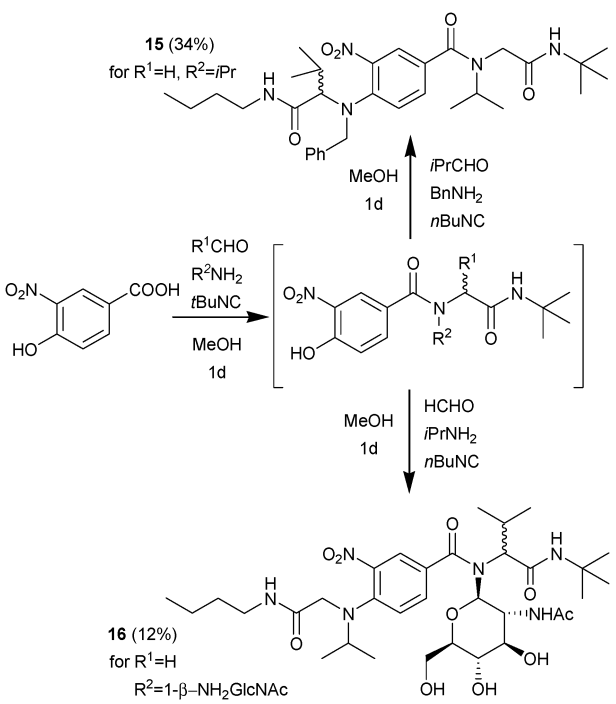
the Ugi–Mumm to the Ugi–Smiles was studied. It turned out that the Ugi–Mumm product **13** is formed in 91%, the Ugi–Smiles product **14** in only 7% (Scheme 3). The structures were assigned unambiguously by HMBC experiments.

Based on this considerable degree of chemoselectivity, the possibility was explored to carry out the reactions sequentially in one pot, with the Ugi–Mumm reaction first and the Ugi–Smiles reaction second (Scheme 4).

After adding a first set of Ugi-starting materials (formaldehyde, isopropyl amine and *tert*-butyl isonitrile), a second set of Ugi-components (isobutyric aldehyde, benzyl amine and *n*-butyl isonitrile) is added after 24 h, upon which the mixed Ugi–Mumm/Ugi–Smiles product **15** can be isolated as a



Scheme 3 Competitive experiment of Ugi–Mumm and Ugi–Smiles reaction.



Scheme 4 Seven-component reactions leading to highly diverse products.

racemate in 34%, reflecting a >85% yield for each bond forming step (eight bonds formed). While using 1-β-amino-GlcNAc as the amine component, the desired glycoconjugate **16** can be isolated as a mixture of diastereomers (3 : 1) in 12% yield. Most notably, the carbohydrate moiety can be used without any protecting group.

The reactions presented here are examples of tandem Ugi-MCR's based on the chemoselectivity provided by the acidic component. This will be utilized *inter alia* in further studies concerning the synthesis of highly diverse glycoconjugates by easy to carry out protocols.

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