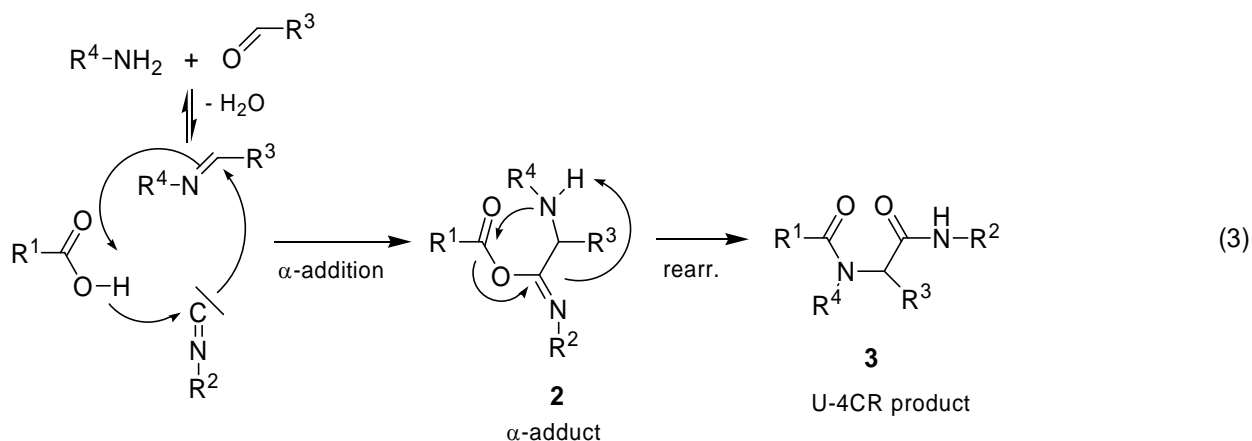


Multi-Component-Reactions (MCRs)

MCR chemistry^{3,21} has a rather long tradition in pure and applied chemistry. First MCRs have been established up from 1850, as are the Strecker- (S-3CR), Hantzsch- (H-3CR), and Mannich-reactions (M-3CR). Thereby important compounds as α -amino acids or dihydropyridine derivatives have been synthesized in one-pot-reactions. Problems with these reactions may be, that they are more or less reversible. But the isocyanide-based I-MCRs as Passerini- (P-3CR)^{1-3, 21} and Ugi-reactions (U-4CR)^{1-3, 21} (3), undergo in the last step an irreversibly intramolecular rearrangement reaction of their α -adducts **2**, namely highly reactive azaanhydrides, with the nucleophilic intermediates hydroxy- or amino-groups to form the corresponding α -hydroxy- or α -amino-carboxylic acid amides **3**. Thereby the change of the formal C^{II}-carbon in the isocyanides to the C^{IV}-carbon in the products plays the important role in irreversible forming products within the last step. Beyond this, addition reactions in general are preferable reactions in syntheses, because they are not accompanied by coproducts as are in substitution or elimination reactions. Facit: Decreasing reaction steps and irreversible forming of products makes isocyanide-based MCRs to highly efficient reactions in the view of achieving high yields over several steps.

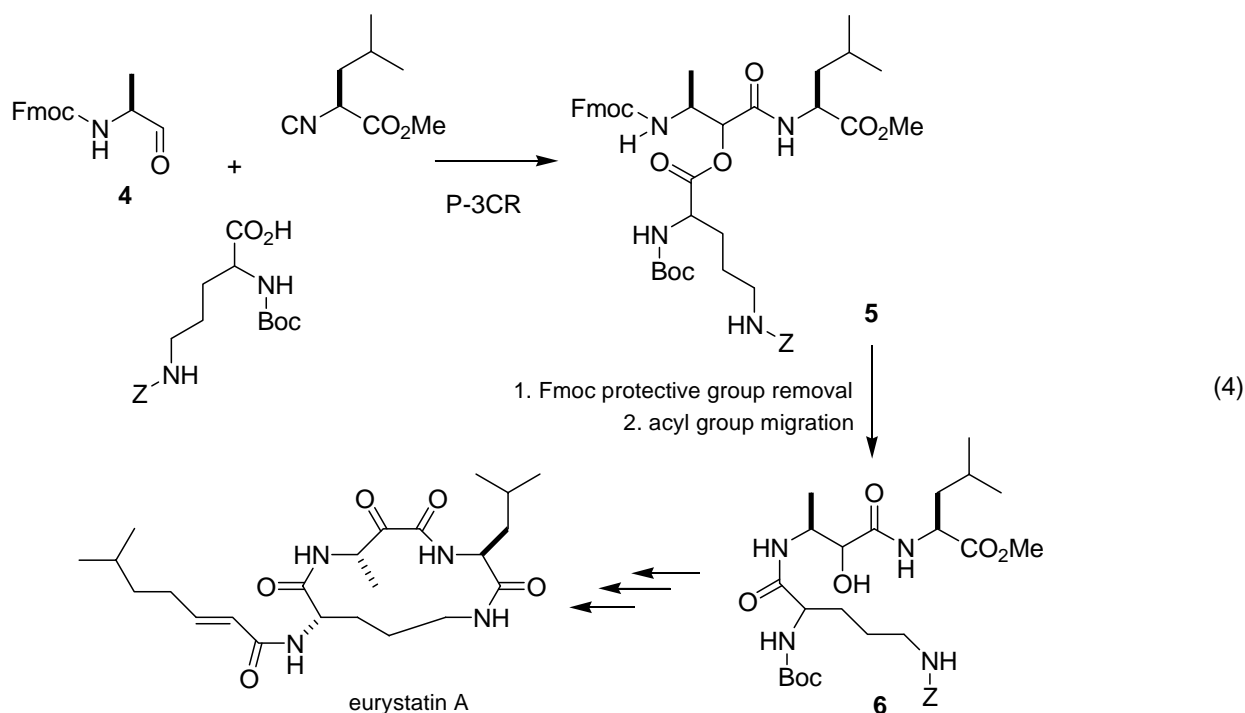


Particularly the Ugi-reaction has proven to be the most versatile MCR³, the number of publications on it has been increased strongly since about the year 2000. Isocyanide-based MCRs as Ugi- and Passerini

reactions have been employed successfully in the preparation of compounds as natural products,^{2,4} amino acids, peptides and peptoides,⁵ heterocycles,⁶ macrocycles,⁷ drugs and pharmaceuticals,^{2,8} interesting organic compounds⁹ (polysaccharide hydrogels,^{9b} butenolides^{9c}), and substance libraries.¹⁰ Also new synthetic methods based on these reactions have been developed in total synthesis¹¹ (Ecteinascidin 743^{11a} and Eurystatin A^{11b}), post-condensation modifications,¹² protein mimicry,¹³ stereo selective reactions,¹⁴ macrocyclization,⁷ acceleration of synthetic diversity,¹⁵ and combination of MCRs with enzymatic methods.¹⁶ Thereby recent working areas as combinatorial chemistry,^{17, 10} and green chemistry¹⁸ based on Passerini- and Ugi-reactions have been interfused by innovative methods¹⁹ (U-4CR and ketene [2+2] cycloaddition,^{19a} O- and N-aryl amides in MCR-products^{19b}, metal-mediated Passerini-reactions,^{19c} aqueous medium effect on MCRs^{19d}) and creative techniques²⁰ (ionic liquids as solvent,^{20a} microwave heating,^{20b} fluoros synthesis,^{20c} solid-phase reactions,^{20d} high pressure reactions^{20e}). A comprehensive book on Multicomponent Reactions³ and some reviews²¹ are summarized.

Post-Condensation Modifications

The enormous synthetic possibilities of I-MCRs can be enlarged by post-condensation modifications.¹² Thereby difunctionalized components, if necessary attached with a protective group, as **4**, are employed in a MCR. After accomplishing the MCR, the remaining function, if necessary after cleavage of the protection group, is reacted with additional reagents in a consecutive way. Thus further synthetical steps as macrocyclization can be performed. A notable example for this method is the total synthesis of Eurystatin A by a novel Passerini reaction--deprotection--acyl migration strategy^{11b} (**4**). The P-3CR product **5** is liberated from Fmoc-residue, whereas the vicinal acyl group migrates to form **6**.

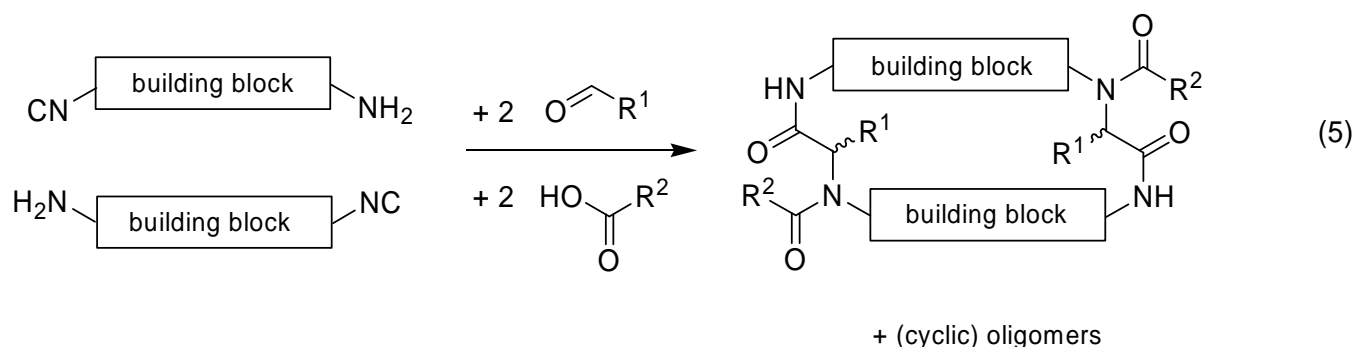


Bifunctional Building Blocks

The bifunctional components from above (2) can also be employed without protective groups to react at both sides of the building block **1** within a MCR, as already shown in a typical synthesis of heterocycles and drugs azetidinones, where **1** contains an amino- and a carboxylic acid group as two functions reacting in a U-4CR (2).

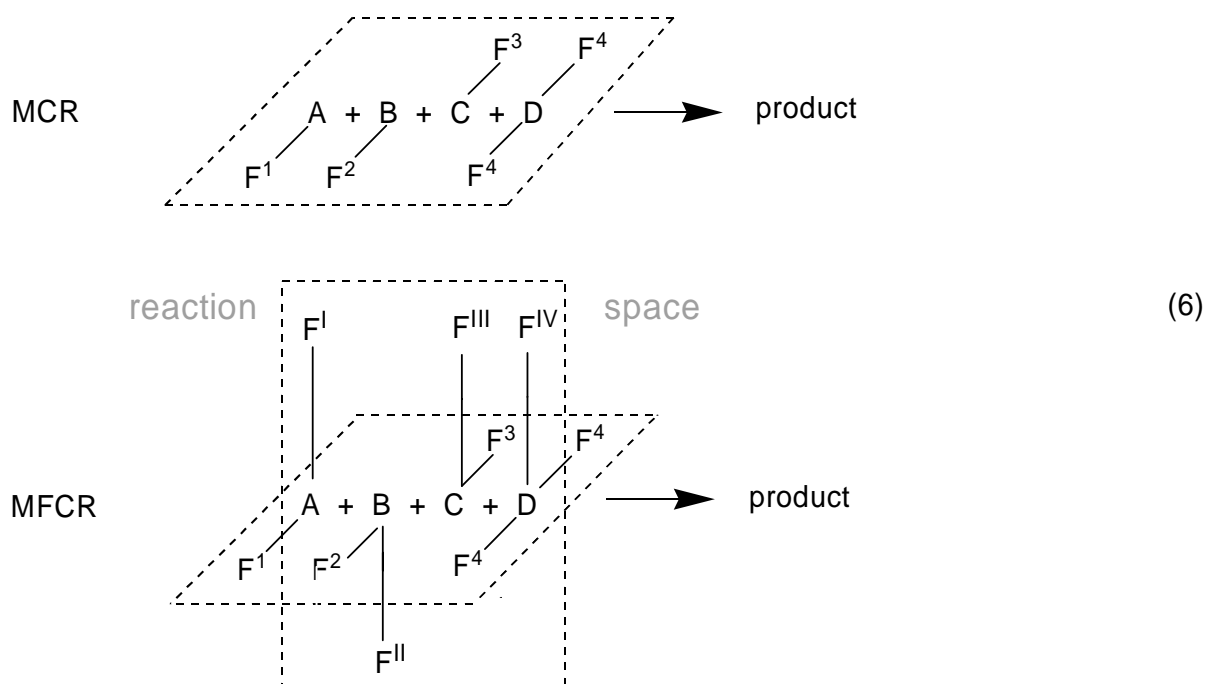
Multiple Multi Component Macrocyclizations including Bifunctional Building Blocks (MMMiBBBs or MiBs)

Using two components each with two reactive functional groups as bifunctional building blocks, macrocyclizations⁷ can be performed by reacting both building blocks. Inside the building blocks the functional groups can vary; diamino, diisocyano, dicarboxylic acid and mixed functions building blocks have been employed together with the complementary components in the corresponding U-4CRs in order to carry out macrocyclizations as shown in an example of a Ugi-MiB according to equation (5).^{7a}

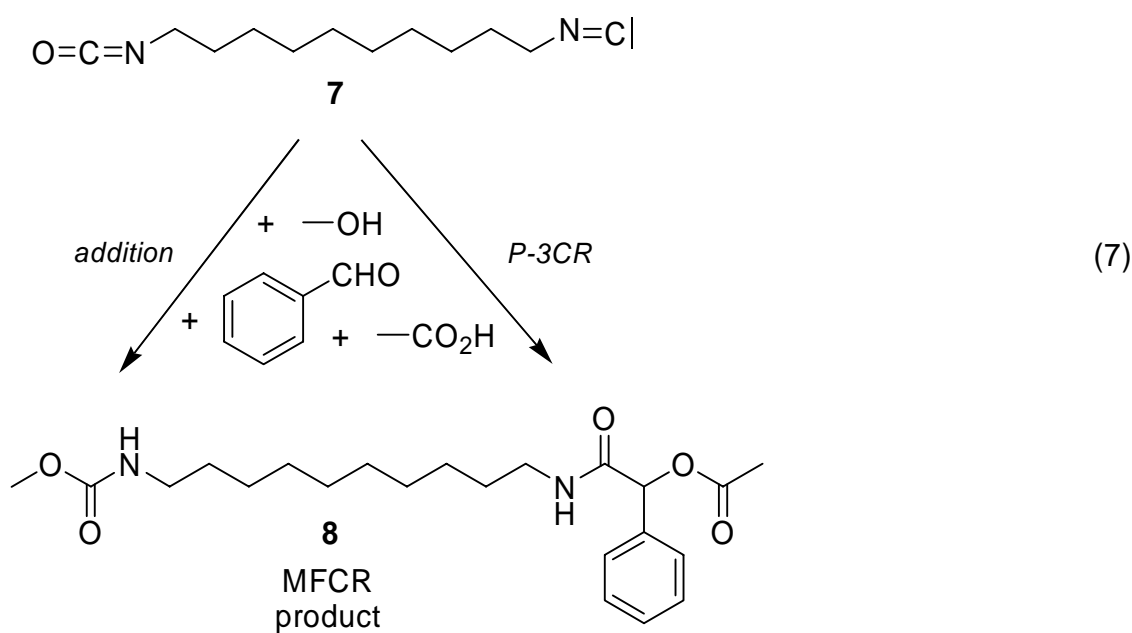


Multi-Function-Component-Reactions (MFCRs) as Parallel Reactions

A further acceleration of the synthetically valuable possibilities of MCRs as there are less reaction steps and higher structural diversity, it is advantageous to add further orthogonal functions to the components, which react in parallel reactions simultaneously alongside the MCR with other external groups (or with intermediate functions generated by the MCR) in a one-pot-reaction, but not in a consecutive strategy (as in post-condensation modifications, see above). Only thus the great advantages of MCRs can be maintained inherent to the system. The result is a novel reaction type, the Multi-Function-Component-Reaction (MFCR). To clarify this, MCR and MFCR are illustrated in (6): all functions $F^1 - F^4$ of the MCR are arranged in the same plane, the additional orthogonal functions $F^1 - F^{IV}$ are depicted in the plane orthogonal to the first. The orthogonal functions open a new dimension within the reaction space.



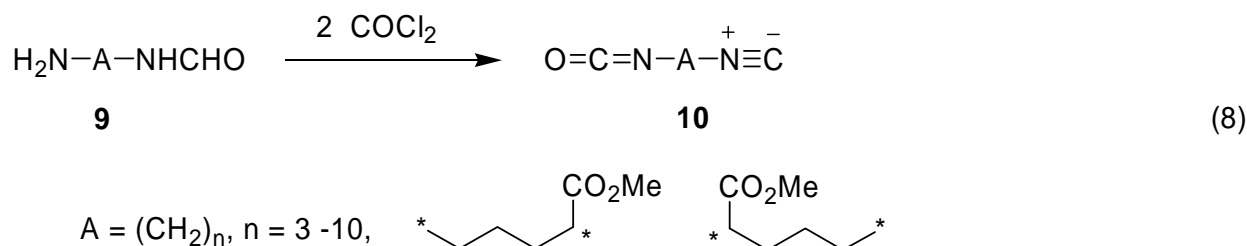
This has been demonstrated in simultaneous parallel reactions of the isocyanato-isocyanide component **7** (see also the chapter below) with benzaldehyde and acetic acid components in a P-3CR, and of methanol in an addition reaction with the isocyanate group of **7** in a one-pot-reaction, providing the MFCR (P-3CR + carbamate) product **8** in good yield of 92 % (**7**).²²



Isocyanato-isocyanides (I-Is)

The key-role in Ugi- and Passerini-reactions plays the isocyanide function,¹⁻³ as pointed out in the above

chapter about I-MCRs. To achieve the preconditions of MFCRs from the foregoing chapter, particularly the orthogonal reactivity of functions at a bifunctional component and both functions high reactivity, isocyanato-isocyanides (I-Is) **10** have been created and easily prepared from amino-formamides **9** by both carbonylation and dehydration reactions with phosgene in a one-pot-reaction in yields of 50-80 % (8).²²



The I-Is are the exceptional case of a highly reactive electrophilic functional group (isocyanate) and a highly reactive nucleophilic functional group (isocyanide) at the same molecule. I-Is were unknown up to now and are astonishingly stable; they can be stored in a freezer for several weeks, above about 90 °C they decompose. They can also be employed into a MFCR freshly prepared without purification.

Outlook

To enhance further the efficacy of MCRs, three movements will be probable:

- 1) increase of components within MCRs,
- 2) increase of orthogonal functional groups at each component and thus creating large MFCRs,
- 3) increase of parallel reactions within the MFCRs according to 2),

which will make possible a creation of countless compounds, particularly heterocycles, with exactly defined structure of high-grade diversity.

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