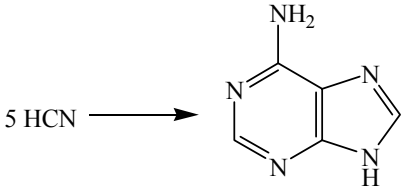
1.2 Multicomponent reactions

A multicomponent reaction (MCR) is a process in which three or more easily accessible components are combined together in a single reaction vessel to produce a final product displaying features of all inputs and thus offers greater possibilities for molecular diversity per step with a minimum of synthetic time and effort.
A MCR is a domino process, a sequence of elementary steps according to a program in which subsequent transformations are determined by the functionalities produced in the previous step.
MCRs constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses. Coupled with high-throughput library screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds. Libraries of small-molecule organic compounds are perhaps the most desired class of potential drug candidates, because standard peptides and oligonucleotides have limitations as bioavaliable therapeutics.[2, 11, 12] With a small set of starting materials, very large libraries can be built up within a short time, which can then be used for research on medicinal substances.

In spite of the significant useful attributes of MCRs for modern organic chemistry and their suitability for building up large compound libraries these reactions were of limited interest in the past fifty years. However, in the last decade, with the introduction of high-throughput biological screening, the importance of MCRs for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focussed especially on the design and development of multi-component procedures for the generation of libraries of heterocyclic compounds.[13] This growing interest is stimulated by the significant therapeutic potential that is associated with many heterocycles. Furthermore, the utility of the rigid well-defined structures of heterocycles was demonstrated in many detailed structure activity relationship (SAR)-studies.[14]

1.2.1 History of Multicomponent Chemistry

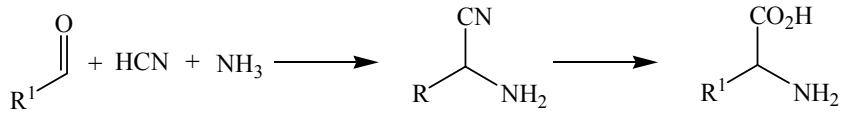
The concept of MCRs is not unknown in nature, it is important especially in evolution. It seems that adenine **10**, one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN, a plentiful component of prebiotic atmosphere, in a reaction catalyzed by NH_3 (Scheme 5).[15-19] The other nucleic bases have been generated in similar reactions involving HCN and H_2O.



10

Scheme 5 Prebiotic synthesis of adenine

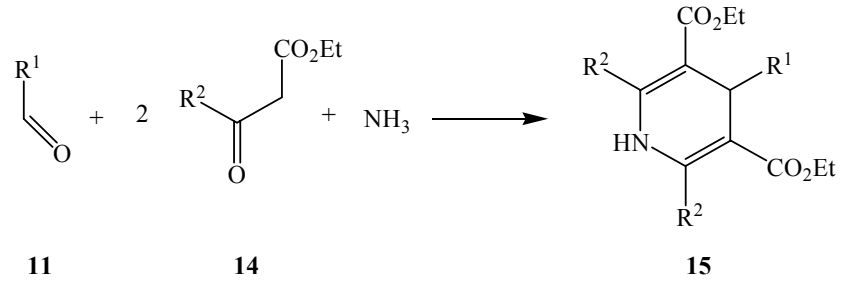
The first modern contribution to the development of multicomponent chemistry was made in 1850 by Strecker. The crucial step in the well-known Strecker synthesis of α-amino acids is the formation of α-amino nitriles **12** from aldehydes **11**, HCN and NH_3 in one-pot.[20] Subsequent hydrolysis of these synthetically valuable intermediates results in the amino acids **13**.



11 **12** **13**

Scheme 6 Strecker synthesis of α-amino acids

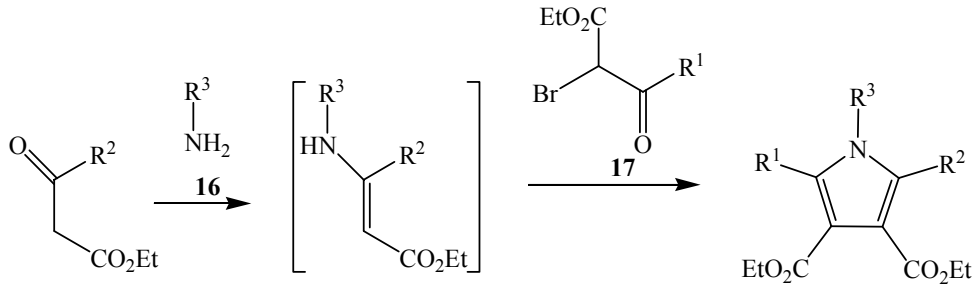
Further progress of multicomponent chemistry can be attributed to the work of Hantzsch in 1882. He synthesized symmetrically substituted dihydropyridines **15** from NH_3, aldehydes **11** and two equivalents of β-ketoesters **14**.[21]



11 **14** **15**

Scheme 7 Hantzsch multicomponent synthesis of dihydropyridines

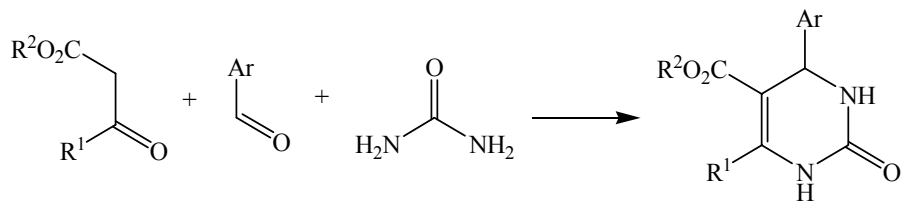
Another contribution made by Hantzsch to MCRs was the synthesis of pyrroles **18** by reacting primary amines **16**, β-ketoesters **14** and α-halogenated β-ketoesters **17**.[21]



14 **18**

Scheme 8 Hantzsch multicomponent synthesis of pyrroles

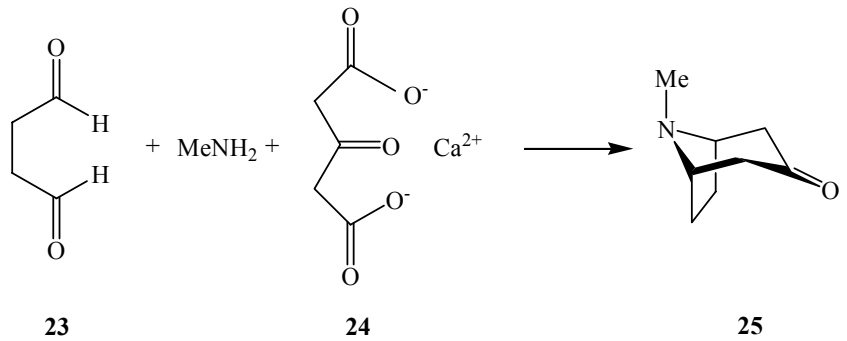
The Biginelli reaction first described in 1893 represents multicomponent synthesis of substituted dihydropyrimidines **22** by acid-catalyzed cyclocondensation of β-ketoesters **19**, aromatic aldehydes **20** and urea **21**.[22-25]



19 **20** **21** **22**

Scheme 9 Biginelli multicomponent synthesis of dihydropyrimidines

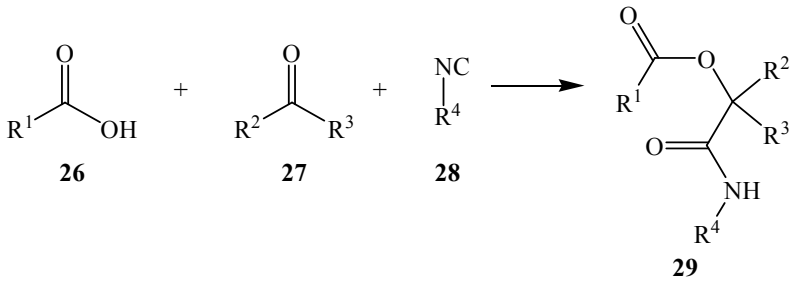
The first important application of MCRs in natural product synthesis was the Robinson synthesis of the alkaloid tropinone **25** from succinic dialdehyde **23**, methylamine and calcium salt of acetonedicarboxylic acid **24**, carried out in 1917.[26]



23 **24** **25**

Scheme 10 Robinson synthesis of tropinone

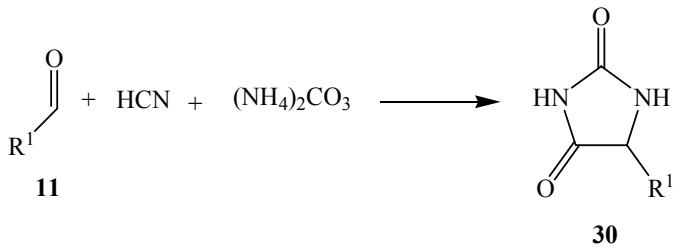
The first MCR involving isocyanides was discovered in 1921 by Passerini.[15] Carboxylic acids **26**, carbonyl compounds **27** and isocyanides **28** afforded α-acyloxy carboxamides **29** in a one-pot procedure.[17, 27]



26 **27** **28** **29**

Scheme 11 Passerini 3-component reaction

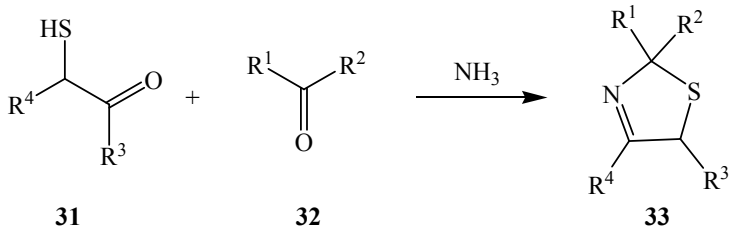
In 1934 Bucherer and Bergs described a four-component reaction for synthesis of hydantoins **30**. One-pot reaction of hydrogen cyanide, aldehydes **11**, NH_3 and CO_2 afforded hydantoins,[28] which can be easily transformed into α-amino acids by simple hydrolysis.[29, 30]



11 **30**

Scheme 12 Bucherer-Bergs multicomponent synthesis of hydantoins

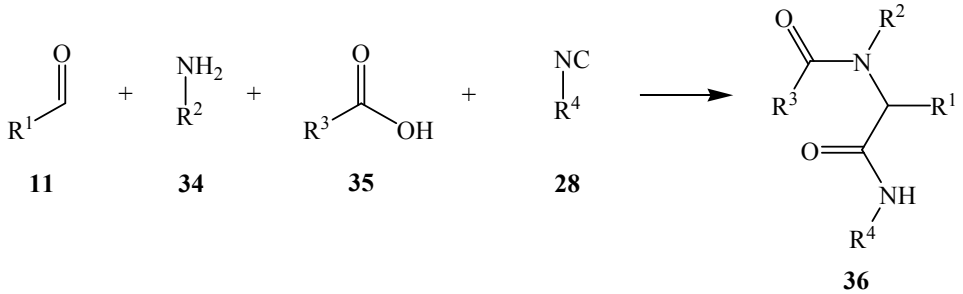
The next important example is the Asinger reaction reported in 1958. α-Halogenated carbonyl compounds and sodium hydrogen sulfide generated *in situ* thiols **31** which reacted with carbonyl compounds **32** and ammonia to afford thiazolines **33**.[31]



31 **32** **33**

Scheme 13 Asinger reaction

One of the most utilized multicomponent reactions was discovered in 1959 by Ugi et al.[17] Synthesis of α-acylamino amides **36** was achieved by reacting aldehydes **11**, primary amines **34**, carboxylic acids **35** and isocyanides **28**.[17-19, 27]

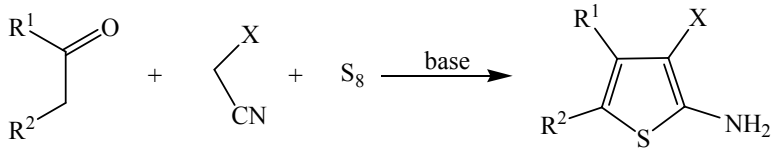


11 **34** **35** **28** **36**

Scheme 14 Ugi-four component reaction

In 1961 Gewald and co-workers described the synthesis of polysubstituted thiophenes **38** with electron withdrawing substituents such as cyano, carboethoxy and carboxamido in the 3-

positions and alkyl, aryl, cycloalkyl and hetaryl groups in the 4- and 5-positions. Three major modifications of this method are described in literature which give access to various 2-aminothiophenes.[32] The most elegant and simplest version consists of a one-pot procedure which includes the condensation of aldehydes, ketones or 1,3-dicarbonyl compounds with activated nitriles **37** and sulfur in the presence of amine at room temperature. Ethanol, methanol, dimethylformamide, dioxane, excess ketone such as methyl ethyl ketone or cyclohexanone are preferred solvents and the most often employed amines are diethylamine, morpholine or triethylamine.



37 **38**

Scheme 15 Gewald's reaction

1.2.2 Isocyanide multicomponent reactions and isocyanides

A large and important class of MCRs are the isocyanide multicomponent reactions, first of them was introduced in 1921 by Passerini.[15, 16] One of the most significant advantages of isocyanide based MCRs are their compatibility with a range of ancillary functional groups not taking part in the initial MCR. Of particular relevance to complex synthesis is the planned possibility that such functional groups can then be utilized in a secondary reaction through various methodologies.

Isocyanides (isonitriles) are compounds with an extraordinary functional group and unusual valence structure and reactivity. Isocyanides represented for a long time the only class of stable organic compounds with a formally divalent carbon. Owing to its reactivity the isocyanide group differs fundamentally from other functional groups. The chemistry of isocyanides is characterized by three properties: the α-acidity, the α-addition and the easy formation of radicals.

The isocyanides are also well-known for their strange odour. Almost all commercially available isocyanides are volatile and carry this repulsive odour "which is reminiscent of

artichokes and phosphorus at the same time".[33] Prolonged inhalation of isocyanides is believed to increase the intensity of dreams at night.[27]

Isocyanides were first synthesized in 1859 by Lieke, who first believed them to be nitriles.[34] In 1867 Gautier discovered the isomeric nature of relationship between the isocyanides and the nitriles.[35] A new approach to isocyanides by reacting primary amines with potash and chloroform was developed by Hoffman. The preparative ability and nontrivial work (due to their reactivity, toxicity and odour) may have been the reasons why the chemistry of isocyanides was neglected for one century. The most utilized method for the preparation of isocyanides today is the reaction of the N-formamides with phosgene or phosgene surrogates such as di- and triphosgene or other inorganic dehydratants and matching bases.[36, 37]

Improved availability of isocyanides enabled in 1959 the discovery of the Ugi four-component reaction. In 1960 the Bayer AG company carried out the toxicological examinations of hundreds of isocyanides that proved this class of compounds to be only slightly toxic, apart from few exceptions.[27]

While the Ugi reaction is an excellent tool for a library synthesis, it suffers from a lack of commercially available isocyanides. Unlike the other three readily available components, somewhat fewer than 25 isocyanides can be purchased, limiting potential libraries at R^4 position (Scheme 14). Besides four commercially available isocyanides (benzyl, *n*-butyl, 1,1,3,3-tetrametylbutylisocyanide and methyl cyanoacetate) employed in this work, two isocyanides, cyclohexenyl- and *p*-methoxyphenylisocyanide) have been synthesized according to previously described procedures[38, 39] and applied in Ugi-type multicomponent reactions.