Multicomponent Reactions

One of the major challenges in today’s synthetic chemistry is the establishment of ideal step-economic processes (multi bond formation in one operation) with regio, chemo and stereo selectivity. Along with regio, stereo and chemo selectivity, an ideal chemical process should satisfy the criteria that it should be a process based on readily available starting material, operationally simple, easily automatable, resource effective, atom economical and ecologically benign. The complexity of organic target molecules is constantly increasing and novel strategies allowing the efficient formation of new carbon–carbon bonds between functionalised moieties are needed. The recent fashion in this scenario is the development of multicomponent reaction (MCR) processes. By definition, multicomponent reactions (MCR) are reaction processes in which three or more reactants are combined in a single chemical step to produce products that incorporate substantial portions of all the components reacted.

Multicomponent reactions are particularly effective at building functionalised drug-like structures from different families of compounds in a single step. Inventing and developing new MCR processes are important pursuits in academic, industrial and pharmaceutical chemistry. The last few years have seen a revolution in the development of new MCR reactions focused on the synthesis of enantiomerically pure or enriched compounds based on the use of new reagents and catalysts.

In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent,
temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.

**Figure 1. Schematic presentation of a divergent one component reaction, a two component reaction and a highly convergent six component reaction.**

In the light of chemical productivity and generation of molecular diversity an “ideal” MCR should, not only comprise more than two starting materials but also these starting materials would be different and all or most of the atoms of those starting materials would be incorporated into the final product.

Most of the known older multicomponent reactions have been found by serendipity rather than by rational planning. It is interesting to note that many of them are constructed from only a few “prototypic” reactions that include amines and carbonyl functions of different reactivities like aldehydes, ketones, carboxylic acids, esters and amides – the main repertoire of chemists of those days. With the emerging automation of synthesis, purification and analysis in the area of combinatorial chemistry, we are entering into a new phase of our synthetic capabilities. New techniques like coupling liquid chromatography, mass spectroscopy and nuclear magnetic resonance (LC-MS-NMR) allow performing the fast and exhaustive investigation of rather
crude reaction products that may lead to new insights into "old" reaction mechanisms.

The parallel synthesis of large libraries of pure single compounds has been established in many pharmaceutical and agrochemical companies over the last years. Many otherwise "known" reactions have been investigated and used with a so far unseen wide range of starting materials, providing both insights into the breadth of these reactions as well as tales of the unexpected.

Carbonyl compounds played a crucial role in the early discovery of multicomponent reactions, as displayed by a number of following named reactions. The various multicomponent reactions involved by the carbonyl compounds are shown in Scheme 1.

**Scheme 1. Multicomponent reactions of carbonyl compounds.**

**Biginelli reaction**

\[
\text{EtO}_2\text{C} - \text{Me} - \text{CO} + \text{HCO} + \text{H}_2\text{N} - \text{CO} \xrightarrow{\text{H}^+ \text{ EtOH, } \Delta} \text{EtO}_2\text{C} - \text{Me} - \text{N} - \text{H} - \text{N}
\]

**Bucherer-Bergs reaction**

\[
\text{O} = \text{C} - \text{R} \xrightarrow{\text{KCN, } (\text{NH}_4)_2\text{CO}_3} \text{O} = \text{C} - \text{R}'
\]

**Gewald reaction**

\[
\text{R} - \text{C} - \text{R}' + \text{N} - \text{C} - \text{D} - \text{OR}'' + \text{S}_8 \xrightarrow{} \text{H}_2\text{N} - \text{S} - \text{R}'
\]
Hantzsch Dihydropyridine (Pyridine) synthesis

\[ R-CHO + 2R\text{--}\text{COOR} + \text{NH}_3 \rightarrow \text{R}^\text{''}\text{COC} + \text{COOR}^\text{''} \]

Kabachnik-Fields reaction

\[ R\text{--}\text{R'} + \text{R''NH}_2 + \text{HPO} + \text{OR}^\text{''} \rightarrow \text{R}^\text{''}\text{P} + \text{OR}^\text{''} \]

Mannich reaction

\[ \text{H} + \text{R}_2\text{NH} + \text{R}\text{--R'} \rightarrow \text{R}_2\text{N} + \text{R}^\text{'}\text{R}^\text{''} \]

Strecker synthesis

\[ \text{R}+\text{NH}_3/\text{HCN} \rightarrow \text{R}\text{--NC} \rightarrow \text{R}\text{--NH}_2 \rightarrow \text{R}\text{--COOH} \]

Kindler thioamide synthesis

\[ \text{C} + \text{S}_0 + \text{HN} \rightarrow 130^\circ \text{C}, 3 \text{ h} \rightarrow \text{TsOH} \]

Multicomponent and sequential one-pot processes address very fundamental principles of synthetic efficiency and reaction design and they are steadily gaining a considerable and increasing academic, economic and ecological interest. Additionally, the aspect of a modular chemistry of one-pot reactions can be readily expanded into combinatorial and solid phase
syntheses, promising manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts and even novel molecule based materials. Pioneering work by several research groups in this area has already established the versatility and uniqueness of one-pot multicomponent coupling protocols as a powerful methodology for the synthesis of diverse structural scaffolds required in the search of novel therapeutic molecules.

**Microwave Assisted Organic Reactions**

Microwave heating offers remarkable decrease in the time necessary to carry out reactions. It also appears that microwaves have a specific *microwave effect* that lowers the activation energy of reaction. During microwave-irradiated reactions many functional groups do not need protection. Very high yields and clean reaction have been obtained using only small amount of energy. The non-inert atmospheric conditions and simple experimental procedure are additional convenience. Microwave heating allows preparation of number of compounds at the same time in the microwave cavity. Therefore it is very useful in parallel and combinational synthesis. Microwave enhancement can take several forms. Reaction rate can be accelerated activated or suppressed. Fundamentally, microwaves heat things differently than conventional means.

**Mechanism of Microwave heating**

Microwaves are a form of electromagnetic energy lies in the region of the electromagnetic spectrum between infrared waves and radio waves. Specifically they are defined as those waves with wavelengths in between 0.01 and 1 metre, corresponding to frequency of 30 and 0.3 GHz. In order to avoid interference with RADAR equipment and telecommunications, the wavelengths at which industrial and domestic microwave apparatus may
operate is regulated at both national and international levels. In majority of countries 2.40(± 0.050) GHz is the major operating frequency.

As with all electromagnetic radiation, microwave radiation can be divided into an electric field component and a magnetic field component. The former component is responsible for the dielectric heating, which is effected via two major mechanisms, dipolar polarisation and conduction.

**Dipolar Polarisation**: A substance should possess a dipole moment in order to heat when irradiated with microwaves. A dipole is sensitive to external electric field and will attempt to align itself with the field by rotation. The applied field provides the energy for this rotation. For a molecule in polar liquid such as water (methanol, ethanol, THF etc.), there are intermolecular forces, which give any motion of the molecule some inertia. The ability of molecules in a liquid to align with the applied electric field will vary with different frequencies and with the viscosity. Under a very high frequency electric field, the polar molecule will attempt to follow the field, but intermolecular inertia stops any significant motion before the field has reversed, and no net motion results. If the frequency of field oscillation is very low, then the molecule will be polarised uniformly and no random motion results. In the microwave radiation region, the frequency is however, not high enough for the rotation to precisely follow the field. Therefore as the dipoles re-orient to align itself with the electric field, the field is already changing and generates a phase difference between the orientation of the field and that of the dipole. This phase difference causes energy to be losing from the dipole by molecular friction and collisions, giving rise to dielectric heating.

**Conduction mechanism**: A solution containing ions, or even a single isolated ion with a hydrogen bonded cluster, in the sample the ions will move through the solution under the influence of an electric field, resulting in
expenditure of energy due to an increased collision rate, converting the kinetic energy to heat. The conductivity mechanism is a much stronger interaction than the dipolar mechanism with regard to the heat-generating capacity.

**Solvent free organic synthesis**

The chemists, for developing environment-friendly synthetic procedures has made them turn their attention to minimize or circumvent the use of solvents that are the major cause of pollution. It is believed that solvent free organic synthesis and transformation are industrially useful and largely green. This has led, in recent times, to vigorous research activity and reinvestigation of known reactions to achieve organic syntheses under solvent free conditions. The combination of solid support and microwave heating will be of importance in the search for green laboratory scale synthesis. The microwave strategy provides broad scope in the future development of clean and sustainable organic chemistry. Microwave synthesis represents one of the important dimensions of modern chemistry. The use of microwave processing is now the hot topic for combinatorial and parallel strategies.

The solvent free conditions under microwave irradiation, that is Microwave induced Organic Reaction Enhancement (MORE) chemistry offers several advantages. The cleanliness of microwave chemistry does away with the need for a solvent i.e. “The best solvent is no solvent”. The solvents are often expensive, flammable, toxic, difficult to remove in the case of aprotic dipolar solvents with higher boiling points and are environmental polluting agents with disposal is often expensive. Waste solvents are a major problem for the chemical industry. More over liquid–liquid extraction is avoided for the isolation of reaction product.

Solvent free reactions bring down handling cost due to simplification of experimental procedures (only simple glassware needed), work up
technique and saving of labour. Microwave heating allows substantially improved productivity of many chemical processes with reduced formation of byproducts caused by overheating, also reduction in thermal degradation. Solvent less microwave synthesis is a springboard to clean, economical and safe industrial processing.