MULTIDISCIPLINARY RESEARCH

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Multicomponent Reactions Tools for Sustainable Development

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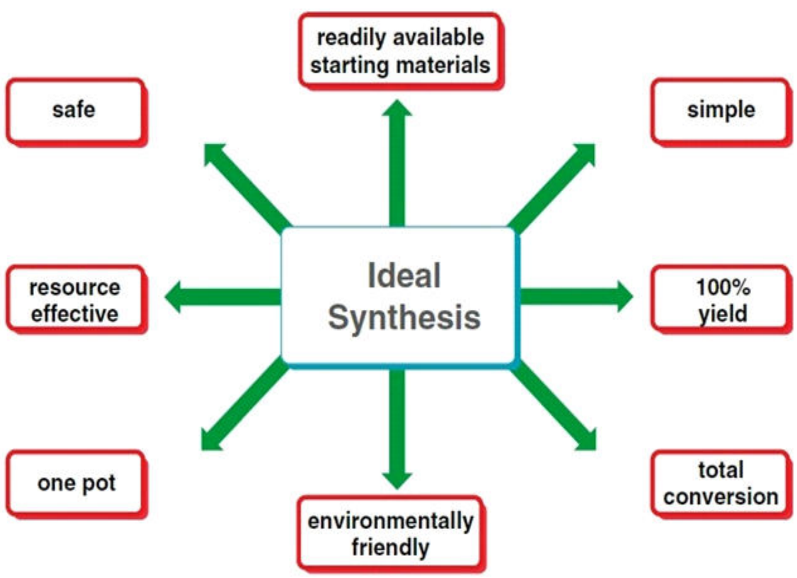
There is a clear need for the discovery and development of clean, atom-economy and step-efficient one-pot syntheses for sustainable production of molecularly diverse and structurally complex organic molecules with high added values. Infact, synthetic strategies are required that can enable the "ideal synthesis" leading to the preferred product from readily available starting materials in a less number of reaction steps and in good overall yield [1].



For the synthesis of fine chemicals, the product /waste ratio ranges between 50 and 5; for pharmaceutical industry, this ratio may even be as high as 100. To ensure the high standards set by the 21st century society such as food, medicines, or materials whenever they are needed, researcher need ways to effectively design and make molecules and produce the materials made from them.

Multicomponent reactions (MCRs) are progressively more appreciated as efficient syntheticprotocol to fast access complex products[2]. In MCRs, moleculescan be assembled from more than two starting materials in a one-pot process. MCRs involve the formation of several bonds in a single operation, without isolating the intermediates, changing the reaction conditions, and often without adding further reagents. Therefore, MCRs address sustainability by step, atom, and eco-efficiency, reducing the number of intermediate stepsand functional group manipulations and avoiding protective group methodologies. Syntheses involving MCRs save time and energy and proceed with high convergence. In addition, MCRs are preferably suitedfor combinatorial chemistry and library design, and are of enormous utility in medicinal chemistry, materials science.

Multicomponent reactions (MCRs) are commonly defined as reactions in which more than two starting materials in the same pot to generate a product. Their utilitycan be reorganized by multiple advantages of MCRs over traditional multistep Protocol. In MCRs, a molecule is assembled inone convergent chemical step in one pot by simply mixing the corresponding starting materials as opposed to traditional ways of synthesizing a target moleculeover multiple sequential steps. At the same time, considerably complex molecules can be assembled by MCRs. This has considerable advantages as it saves precious time and drastically reduces effort. Traditionally, efficiency is encoded in the synthetic chemist'smind mostly in terms of yield, selectivity and number of steps. The green chemistry perspective is, however, considerably broader and includes criteria for waste generation, use of reagents and solvents, use of hazardous chemicals, energy intensity and general safety. All these criteria are assembled inthe set of 12 principles formulated by Anastas and Warner in 1998[3].

- **Prevention:** It is better to prevent waste than to treat or clean up waste after it has been created.

- **Atom economy:** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
- **Less hazardous chemical syntheses:** Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- **Designing safer chemicals:** Chemical products should be designed to effect their desired function while minimizing their toxicity.
- **Safer solvents and auxiliaries:** The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
- **Design for energy efficiency:** Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
- **Use of renewable feedstock's:** A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
- **Reduce derivatives:** Unnecessary derivatization (use of blocking groups, protection/deprotection, and temporary modification of physical/ chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
- **Catalysis:** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
- **Design for degradation:** Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
- **Real-time analysis for pollution prevention:** Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
- **Inherently safer chemistry for accident prevention:** Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Considering those principles that actually relate to chemical reactions, MCRs actually perform very well. For example, MCRs by definition have a perfect atom economy[4]. The reactants for MCRs are typically chosen from a wide range to select lesshazardous inputs. Because of their step economy[5], MCR based syntheses require less solvents and auxiliary substances such as chromatography materials, as the numbers of steps and purifications arereduced. In addition, many MCRs proceed in a wide range of solvents, often including renewable solvents. Most MCRs occur at ambienttemperature or slightly above. MCRs involve the simultaneous formation of many new bonds. With respect to stepwise formation, this generally means that chemo selectivity issues are avoided in MCRs, thus making the use of protective groups redundant. Finally, the vast majorities of MCRs occurs spontaneously or under the influence of a catalyst and no stoichiometric reagents are required. The object of green chemistry is to redesign the way in which chemistsconceive synthesis and in accordance its actions do not essentially focus on the development of novel methods, but rather on alternative sustainable variants to existing ones and, most importantly, different synthetic strategies to consist of environmental considerations as early as possible in the process design stage. MCRs are mostly experimentally simple to perform, often without the need ofdry conditions and inert atmosphere. Molecules are assembled in a convergentway and not in a linear approach using MCRs. Therefore, structure–activityrelationships (SARs) can be rapidly generated using MCRs, since all property determining moieties are introduced in one step instead of sequentially[6]. Lastbut not least, MCRs provide a huge chemical diversity and currently more than300 different scaffolds have been described in the chemical literature. For example, more than 40 different ways to access differentially substituted piperazine scaffolds using MCRs have been recently reviewed[7].

Two decades ago, MCR chemistry was almost generally neglected in pharmaceutical and agro industry, now MCR technology is widely recognized for its impact on drug discovery projects and is allowed by industry as well as academia[8]. An increasing number of clinical and marketed drugs were discovered andassembled by MCR.

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