

MULTICOMPONENT REACTIONS: GREEN HOPE TOWARD SUSTAINABLE DEVELOPMENT

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ABSTRACT

Practicing sustainable chemistry is one of the best ways to address ‘man-made’ environmental perils. The decorum set by the laws of green chemistry can lead us towards mitigating such menace. Multi-component reactions are one such weapon in the armoury of a chemist towards developing and inventing commodities ranging from life-saving drugs to lifestyle products through sustainable synthetic methodologies. Though much advancement is accomplished in developing such reactions, a correlation between ‘environmentally benign operation’ and ‘mere synthesis’ is yet to be realized. Herein, we have tried to highlight the gradual advancement of this procedure and what still needs to be achieved to entice the philosopher within ourselves towards greener thoughts and ideas.

Keywords: Multicomponent Reaction, Green Chemistry, Sustainable Development.

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INTRODUCTION

To make Mother Earth a better place to thrive not for the human race alone but all other living creatures alike, every human has a role to play be it minuscule or mammoth. We, the researchers, in varied fields, are running at a stupendous pace towards achieving newer feats in designing sophisticated devices to make our life smooth, and free from diseases often forgetting the hazards and the strain we are gradually releasing into the space where we thrive. We, the chemists and chemical industries are often blamed for causing such peril. Thus, giving stress on practicing green chemistry is the only way out.¹ Initially it was thought that the concept of green chemistry only calls for managing the pollutant released during the reaction or production but with the mounting toxic excreta, managing them becomes a mammoth and sometimes impossible task. So, the most likely path towards a greener environment is to stop generating such toxins. It is easier said than done as a lot of thinking, logic, innovation, designing, engineering, and application are required for the same. One innovative way of achieving such a goal is Multi-Component Reactions (MCR). MCR or MCAP (see Glossary) is a process of combining two or more reactants under suitable conditions to get a single product without generating any waste. The concept of atom economy (see Glossary), one of the twelve principles of green chemistry, can thus be achieved. Most of us may think of this as a utopian way of explaining MCR but, one must accept the fact that if we want to achieve something in practice, we must stretch ourselves towards ideality.

History

Nature has it all and we, humans, need an eye to identify and mimic her for our sustenance. Ugi and his co-workers have correctly defined MCR as ‘older than life’ while stating that the origin of adenine was presumably from five units of hydrogen cyanide where every hydrogen cyanide plays a distinct role.² The first documented MCR goes way back to the 1850s when Strecker prepared α -cyano amines by condensing, ammonia and hydrogen cyanide with an aldehyde, which was easily hydrolyzable to α -amino acids.³ Utilizing the concept of MCR, researchers gradually started synthesizing various heterocyclic moieties like pyrrole (Hantzsch synthesis), dihydropyrimidine (Bignelli synthesis), and precursors to bioactive alkaloids.⁴⁻⁷ In this regard, the work of Passerini towards the synthesis of various α -acyloxy carboxylic

amides, the iron storehouse of many bacteria, using three-component reactions involving an oxo compound and a carboxylic acid, is worth mentioning.⁸ One of the first reports of condensing four units in an MCR was the preparation of hydantoin (an important precursor of numerous α -amino acids) by Bucherer and Steiner.⁹ Slowly the application of MCR entered the domain of industry in the form of the Roelen reaction where hydrogen, carbon monoxide, and an alkene condense to form an aldehyde.^{2,10} W. Reppe's carbonylation and thiazolidine synthesis by Asinger's group are a big step towards the industrial application of MCR.¹¹⁻¹³

Present Scenario

Until 1969, MCR was mere artistry, where chemists tried to design and condense numerous starting materials to produce a target molecule that had very limited use in industries and the procedure followed may not be that environmentally benign. But with the growing consciousness of environmental pollution, the enforcement of the National Environment Policy Act (NEPA, 1969) in the US, and the formation of the Organization for Economic Co-operation and Development (OECD) consisting of thirty industrialized countries (1980), it was clear that the chemists, as well as the chemical industry, needed to perform towards the wellness of the environment. The concept of atom economy or at least step economy, use of environmentally benign reagents, renewable feedstocks, and biodegradability as a tool for reducing waste production was the need of the hour and MCR could be considered a probable solution to the cause. Scientists now started investigating MCR on the platform of twelve principles of green chemistry applying the basic ideas of multi-component assembly processes such as preparing a library of reactive species for a common core structure (scaffold diversity), attaching various appendages to a particular molecular skeleton (appendage diversity), generation of chiral center (stereochemical diversity). Researchers concentrated mainly on four broad aspects to achieve their goals – a. Refining and improvising on the well-known MCRs based on in-depth knowledge of reaction mechanisms, b. Developing new MCR's using the concept of SRR (see Glossary), c. Combining two or more MCR's in a 'one-pot process' towards new novel MCR's and d. Generation of new MCR's by varying reaction conditions. Simoneau and group re-engineered the four-component reaction (U-4CR) of Ugi using organolithium reagent to produce N-substituted α -amino acid diamides leading to a one-pot, five-component Ugi reaction.¹⁴ Another interesting contribution of the same group is the synthesis of substituted indoles by using a three-component Fischer synthesis.¹⁵ Kumagai and colleagues modified the Patisis (3-CR) reaction by generating 15 unique scaffolds from a single precursor which can undergo seven distinct cyclization processes when it is subjected to various reaction conditions.¹⁶ Some classic examples of SRR are the applications done by Ugi and his group by replacing carbonyl moiety with an imine in the Passerini reaction; they even replaced the carboxylic acid group with various other acidic units to generate a variety of scaffolds.^{17,18} Using various dipolarophiles like dimethyl azodicarboxylate, diethylmesoxalate, phenyl isocyanate, etc., on derivatives of isoquinoline numerous groups managed to synthesize a large number of tricycles, and spiro scaffold.¹⁹⁻²¹ Adamo and co-workers prepared a host of MCRs considering the high reactivity of aromatic aldehydes with 3,5-dimethyl-4-nitroisoxazole, followed by a reaction with doubly enolizable ketones, hydroxylamine, hydrazine, (aza)indoles to give spiroisoxazolines, and diheterocycles.²²⁻²³ A unique strategy was developed for evolving new MCRs by combining into a single pot several MCRs.^{24,25} Ugi and associates first demonstrated that it is possible to combine the Passerini three-component reaction with a five-center four-component reaction of Ugi (U-5C-4CR).²⁶ The entire reaction procedure may not be satisfactory but this was the first step toward diversity-oriented synthesis through MCR. Portlock and co-workers in 2003 showed the viability of combining Ugi 4CR and Patisis 3CR MCR's.²⁷⁻²⁸ Paravidino group combined a 4-CR with Passerini 3-CR in one-pot under suitable reaction conditions to prepare depsipeptides with a comparable yield to when prepared separately.²⁹ Using 2-imidazoline and N-(cyanomethyl) amide MCRs, the elder's group not only managed to bring about scaffold diversity but also the complexity within the products formed.²⁵ The procedure demonstrated was unique in the sense that they combined three MCR's to prepare a highly complex structure with 'eleven points of diversity' through an eight-component reaction (8-CR). Combining Ugi and Ugi-Smiles sequentially, Westermann and co-workers managed to prepare the sought product through a single pot seven-component reaction.³⁰ Groebke–Bienaymé–Blackburn three-component coupling reaction of aldehydes, isocyanides, and amino-heteroaromatic compounds lead to

various heterocyclic moieties of pharmacological importance and when such unique molecules are combined with either Ugi or Passerini MCR then it leads to the formation of series of five- and six-component reaction products of high complexity as was shown by Al-Tel and group.³¹ The approaches enumerated till now demonstrate the versatility of MCRs in generating a library of unique scaffolds by bringing about atom/ step economy thus reducing waste.³²⁻³⁵ Probably the best synthetic strategy that can be employed towards greener MCRs is by changing the reaction conditions. It has the added advantage of generating multiple molecular entities from the same starting materials, the basic concept of combinatorial chemistry (see glossary). Chebanov group in 2008 showed that when a cyclic diketone, an aromatic aldehyde, and 5-aminopyroazole are refluxed in ethanol gave a mixture of three products namely pyrazolo[4,3-c]quinolizin-9-ones, pyrazolo[3,4-b]quinolin-5-ones and pyrazolo[5,1-b]quinazolin-8-ones.³⁶ On the contrary, when the same reaction is carried out in presence of NEt₃ under microwave irradiation or conventional heating in a sealed tube at 150 °C gave exclusively pyrazolo[3,4-b]quinolin-5-ones, the thermodynamic product. Maintaining the same reaction condition, if the base NEt₃ is replaced by potassium tert-butoxide or sodium ethoxide, pyrazolo[4,3-c]quinolizin-9-ones become the exclusive product. Application of neutral and room temperature conditions under sonication (see Glossary) lead to the production of pyrazolo[5,1-b]quinazolin-8-ones, the kinetically controlled product only. Another such example of ‘condition-based divergence’ was demonstrated by Elders and colleagues who coupled an aldehyde (or a ketone), a primary amine, and an acidic isocyanide, to yield selectively 2-imidazolines in presence of 2 mol% of AgOAc but when treated with Brønsted acid or using a polar protic solvent yielded oxazoles.³⁷ Use of microwave (MW) in an MCR is a great alternative and proves advantageous to conventional approaches towards atom economy, reaction time reduction, reducing tedious purification process, and high yield, thus paving a path towards a safer, greener alternative. It is possible to produce a large variety of biologically active skeletons having heterocyclic units (acridine, azepines, quinolines, purine, pyrimidine, thiazoles, chromenes, quinazolinone, indole, pyrane, pyridine, pyrrole) through MW assisted MCRs.³⁸ Rising demand for optically pure substances for the agro as well as pharmaceutical industries, the need for designing MCRs was at a high. Metal-mediated MCRs were the main choice for a variety of catalytic enantioselective MCRs but they had their own demerits of abominable metal toxicity thus making the process non-green. Scientists thus introduced various chiral organocatalysts derived from cinchona alkaloids, proline, phenylalanine, certain oligopeptides, phosphoric acid, etc., as a source for induction of chirality and managed to synthesize optically pure derivatives of oxindoles, spirooxindoles, spiropyrazolones, tricyclic chromanes, 3-CR/ 4-CR Passerini type products, Ugi 4-CR type products in an eco-friendly manner.³⁹⁻⁴¹ Some microwave-assisted MCRs have also started showing promises towards bringing about diastereoselectivity in products under a milder reaction condition thus opening up new frontiers for exploration.^{38,42-44} Water being a ‘universal solvent’ is used in many transformation reactions for its easy availability, non-flammability, non-toxicity, and reusability.⁴⁵⁻⁴⁸ For this, an aqueous medium has found its usage in carrying out MCRs.⁴⁷⁻⁵¹ But the major challenge, for water as a reaction medium, is the lack of solubility of many reagents in it thus reducing the efficacy of such reactions. Many research laboratories have come up with a solution to this. They have used surfactants like 10 mol% of SDS in HCl, PTSA under sonication, DBSA, DODAB, DDAB, TBAB, TBAHS, TMAI (for abbreviations see Glossary), 5% Triton X-10 solution in perchloric acid, Triton X-100, cationic surfactant-cetylpyridinium chloride, SO₃H-functionalized ionic liquids in different acids, combined Brønsted acid-surfactant catalysts to bring about ‘micelle-promoted reaction’ in aqueous medium with good atom economy.^{46,49,52} Using the properties of a surfactant like a local concentration in an aggregate, increased solubility of reactants, and introduction of functional groups within the surfactant unit (which can act as a reaction promoter/ enhancer), various well-known MCRs like Ugi, Biginelli, Kabachnik-Fields, Strecker, Hantzsch, Kinugasa were achieved successfully under MCR strategy using aqueous micelle.⁵² Numerous new MCR strategies toward building various heterocyclic scaffolds of pharmacological importance were also envisioned by various research groups using such aqueous micelles with the added advantages of insertion of geometrical as well as optical selectivity into the product formed under ambient reaction conditions.⁵³⁻⁵⁵ Whenever we talk about waste management, and energy efficiency in MCRs, the first thing that comes to our mind is ‘catalysis’. In multi-component reactions, a large array of chemical substances are in use for such catalytic activity starting from simple acids to organocatalysts, metal complexes, heterogeneous catalysts, nanoparticles, and biocatalysts.

Each type has its own merits and drawbacks. But biocatalysts are unique of all in practicing sustainable green MCR chemistry for their ease of degradability, reusability, non-toxicity, and capacity to induce chirality.⁵⁶⁻⁵⁸ Using *Escherichia coli* whole cells, *Saccharomyces cerevisiae*, trypsin from porcine pancreas, *Rhizopus oryzae* lipase, fermenting baker's yeast, *Candida antarctica* lipase, acylase I (aminoacylase) from *Aspergillus melleus*, etc., as biocatalyst, chemists were able to perform several name reactions as well as a variety of three, four, and five component reactions.⁵⁹

Future Perspective

Despite major innovative advancements in MCRs being achieved in the laboratory much needs to be done yet. The knowledge behind trapping of various reactive intermediates generated during the course of an MCR with external electrophiles for developing new bioactive scaffolds essential for new drug designing is still inadequate. Various cycloaddition reactions using 'click-chemistry' has not properly taken off as yet. Developing new MCR's using environmentally benign conditions like the use of green solvents (water/ ionic liquid/ polyethylene glycol), aqueous micelles, solid-phase (silica gel/ alumina gel/ clay), in a milder reaction condition (room temperature/ microwave/ sonication) will always remain a challenge.³⁵ Catalysts certainly play a major role in MCRs but most of them are not environmentally benign. So, the need for biocatalyst (biodegradable and reusable) is a necessity. Loads of investigation using biocatalyst are very much required followed by proper implementation in various industries (polymer, corrosion resistance, nano, medical) to access the full potential of MCRs. Though the introduction of stereo-specificity is a priority for any agro, cosmetics, and pharmaceutical industry, it has been achieved only in a handful of MCRs, and that too mostly at the laboratory level. Purification during the course of an MCR is another frontier where much needs to be done.⁶⁰ Attempts to enhance the efficacy of MCRs that can integrate generation, extraction, and purification of the product in one-pot is still in their infancy. If molecular modeling of all MCRs is done before laboratory application it will definitely be easier to reduce the hazards of chemical pollution substantially. Apart from the above challenges, scaling up from laboratory to industry demands achieving even more. Reduction of reaction time, restriction in solvent usage, and lowering the number of protection-deprotection steps are some of the criteria around which new research towards the development/ invention of MCRs should revolve around, in order to generate a cost-effective, environmental-friendly initiative. Integrating real-time monitoring of pollutant generation during an MCR procedure is in itself a subject of research. Nurturing young brains in the undergraduate levels by including classroom activities, and involving them in higher-order thinking will enhance their curiosity and a better understanding of scientific concepts.⁶¹⁻⁶² This will definitely bring about newer thoughts and ideas to achieve the elusive 'ideal MCR'.

Important Questions

- Can MCR be a solution to reducing waste?
- Can bio-catalyst, aqueous micelle, microwave, ultrasound, and photolysis rise up to the cause of green MCR procedures?
- Can an MCR lead to the synthesis of stereospecific rather than stereoselective products using various environmentally friendly chiral reagents to reduce the generation of undesired products which amount to waste?
- For the success of such a project isn't it necessary to bridge academic institutions and industries?
- Is it possible to integrate real-time pollution analysis with an MCR procedure to develop a green industrial procedure?
- After taking care of all the criteria of waste management, can MCR ultimately be a financially viable alternative for industrial production?
- Is it possible to design an academic curriculum in such a way that it motivates young brains to come up with newer concepts on green MCRs?

CONCLUSION

Since its inception, the multi-component reaction has come a long way and established itself as a valuable weapon in the armoury of chemists to reduce the hazards of pollution and has the inherent capacity to work hand-in-hand with other environmentally benign technologies to bring forward newer concepts to attain more sustainable development methodologies both in laboratories and in industries. The transition from

laboratory to the industry can be smoother if the government shows greater involvement by taking the initiative to provide incentives in any form to the industries if they implement new greener techniques.

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