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Diversity/Target Oriented Synthesis of Complex Molecules via Multi-Component Reactions

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Editorial

The rapid generation of diverse sets of complex molecules can be achieved by employing diversity oriented synthetic strategies in combination with so called complexity generating reactions. Multicomponent reactions (MCRs) have been emerged as an extremely powerful tool in combinatorial chemistry and drug discovery, since it offers significant advantages over conventional linear step syntheses, in terms to improve classical organic reactions, promote new reactions and develop straightforward synthetic routes for bioactive heterocycles [1] and natural products [2]. MCRs are convergent reactions in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. In MCRs, 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 multicomponent reactions in such a way that the network of pre-equilibriated reaction 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. In a true sense, these represent environmentally friendly processes by reducing the number of steps, energy consumption, and waste production. MCRs play an important role in combinatorial chemistry because of its ability to synthesize small drug-like molecules with several degrees of structural diversity. A MCR is defined as three or more different starting materials that react to form a product, where most, if not all of the atoms are incorporated in the final product. This reaction tool allows compound to be synthesized in few steps and usually in a one-pot operation [3]. Another typical benefit from these reactions is simplified purification, because all of the reagents are incorporated into the final product.

MCRs receive increasing attention because they address both diversity and complexity in organic synthesis. Thus, in principle diverse sets of relatively complex structures can be generated from simple starting materials in a single reaction step. The ever increasing need for optically pure compounds for pharmaceutical and agricultural applications as well as for catalysis promote the development of asymmetric multicomponent reactions. In recent years, asymmetric multicomponent reactions have been applied to the total synthesis of various enantiopure natural products and commercial drugs, reducing the number of required reaction steps significantly. Although many developments in diastereoselective MCRs have been reported, its applications in the field of catalytic enantioselective synthesis has just started to blossom. Significantly broadened scopes, new techniques, more environmentally benign methods and entirely novel MCRs reflect the increasingly inventive paths that synthetic chemist follow in this field. Till date, majority of catalytic enantioselective MCRs have been represented by transition metal-catalyzed pathways. However, metal contamination is highly undesirable for drug synthesis. The emergence of organocatalysis greatly influences the quest for new asymmetric MCRs [4].

MCRs have been known for over 150 years. The first documented multicomponent reaction was the Strecker synthesis of α-amino cyanides in 1850, from which α-amino acids could be derived. The chemistry of such reactions and isocyanides belongs to three periods: In the century 1859-1958, isocyanide chemistry was moderately active and was separate from the classical name reactions of the MCRs. In the next period, isocyanides became well available, and MCRs of isocyanides emerged out as most variable way of forming chemical compounds. The year 1993 began a new era of the formation and investigation of the products and the libraries of the Ugi reaction (U-4CR) and higher MCRs of the isocyanides. This chemistry is primarily accomplished in the industrial search and preparation of new pharmaceutical and plant-protecting products. Ugi reaction is an isonitrile-based MCR that provides a rapid route for the preparation of α-aminoacyl amide derivatives. Ugi 4-component condensation of an amine, oxo compound, carboxylic acid and an isocyanide is the most documented and versatile MCR.

Combined with combinatorial chemistry, using the Ugi MCR approach to develop a library of novel compounds and screen against known antimalarial pharmacophores. The library consisted of amino quinoline containing α-aminoacyl amides that were used in structure-activity relationship (SAR) studies [5]. Ugi/Heck combination works well for high-throughput combinatorial library production of indol-2-ones having four points of diversity. This scaffold is of interest because it shows biological effect as antitumor and tyrosine kinase inhibitor activity [6].

Passerini reaction is another isonitrile-based MCR that yields α-acyloxy carboxamides in a one-pot synthesis from an aldehyde, isonitrile, and carboxylic acid. Of the three components, the carbonyl group is one of the most critical reactants because of the pronounced reactivity of the divalent isonitrile carbon atom towards the C(sp^2) electrophilic center [7]. The traditional Passerini reaction involves an aldehyde in the one pot reaction. In some cases, the aldehydes are not stable or are difficult to handle. Recently, Ngouansavanh and coworkers reported that, in place of aldehydes, alcohols were used and oxidized *in situ* using 2-Iodoxybenzoic acid (IBX) and increases the versatility and the number of compounds available for multicomponent reactions [8].

Biginelli reaction is an acid catalyzed, three-component reaction between an aldehyde, β-ketoester, and urea that produces

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tetrahydropyrimidones, which have potential pharmaceutical applications. This reaction was first reported in 1893 and has increased interest because of the final products close structural relationship to the clinically important dihydropyrimidines [9].

Microwave assisted one-pot three-component synthesis of octahydroquinazolines using ammonium metavanadate [10], Nickel nanoparticle catalyzed one-pot synthesis of polyhydroquinolines via Hantzsch condensation [11], synthesis of 6-thiopyridines using boric acid [12] , molecular sieves [13], and triaryl-pyridines using bismuth triflate [14] have been reported. Baker's yeast catalyzed one-pot three component cyclocondensation leading to value-added heterocycles like 4-thiazolidinones and 4*H*-pyaran have also reported [15].

The control of selectivity, for example chemo- and regioselectivity, is among the most important objectives in organic chemistry. For multi-component reactions involving the simultaneous molecular interaction of three or more components, the issue of selectivity is of particular significance due to the high probability of several potential parallel reaction pathways leading to different product classes. Many different process parameters such as temperature, pressure, solvent, catalyst type, microwave and ultrasonic irradiations, and other factors can be utilized to modulate the selectivity of synthetic transformations.

MCRs make possible the speedy synthesis of molecular libraries that have a high degree of structural diversity. Many of these structures are accessible only after 5-10 steps if at all approached by sequential synthesis. Combinations of different starting materials can produce a variety of products with facility, a process that is of great value in the search for new drugs. MCRs can significantly unclog the bottleneck commonly arising in the HTS (High Throughput Screening) discovery process, which centers on the generation of the molecules.

Various kinds of catalysts like homogeneous, heterogeneous and enzymes, newer techniques like microwave, ultrasonication, and flow chemistry approaches have been utilized for multicomponent reactions to make complex/hybrid molecules as well as natural products. Atom-economy, tandem/cascade reactions, and protecting group free strategies have been advocated as overarching goals in contemporary organic synthesis. Arguably, the concept of multicomponent reactions compare favorably with these trend-setting concepts. We hope that the journal, "Organic Chemistry: Current Research" and its special issue on multicomponent reactions affords great opportunity for synthetic organic chemists.

References

1. KC, Hanko R, Hartwig W, (eds). Handbook of Combinatorial Chemistry. Weinheim, Germany: Wiley-VCH.
2. Toure BB, Hall DG (2009) Natural product synthesis using multicomponent reaction strategies. Chem Rev 109: 4439-4486.
3. Xu LW, Xia CG, Li L (2004) Transition metal salt-catalyzed direct three-component Mannich reactions of aldehydes, ketones, and carbamates: Efficient synthesis of N-protected beta-aryl-beta-amino ketone compounds. J Org Chem 69: 8482-8484.
4. de Graff C, Ruijter E, Orru RV (2012) Recent developments in asymmetric multicomponent reactions. Chem Soc Rev 41: 3969-4009.
5. Musonda CC, Taylor D, Lehman J, Gut J, Rosenthal PJ, et al. (2004) Application of multi-component reactions to antimalarial drug discovery. Part 1: Parallel synthesis and antiplasmodial activity of new 4-aminoquinoline Ugi adducts. Bioorg Med Chem Lett 14: 3901-3905.
6. Umkehrer M, Kalinski C, Kolb J, Burdack C (2006) A new and versatile one-pot synthesis of indol-2-ones by a novel Ugi-four-component-Heck reaction. Tetrahedron Lett 47: 2391-2393.
7. Xia Q, Ganem B (2002) Metal-promoted variants of the Passerini reaction leading to functionalized heterocycles. Org Lett 4: 1631-1634.
8. Ngouansavanh T, Zhu J (2006) Alcohols in isonitrile-based multicomponent reaction: Passerini reaction of alcohols in the presence of O-iodoxybenzoic acid. Angew Chem Int Ed Engl 45: 3495-3497.
9. Kappe CO (1997) A Reexamination of the mechanism of the Biginelli dihydropyrimidine synthesis. Support for an *N*-acyliminium ion intermediate. J Org Chem 62: 7201–7204.
10. Niralwad KS, Shingate BB, Shingare MS (2010) Microwave-assisted one-pot synthesis of octahydroquinazolinone derivatives using ammonium metavanadate under solvent-free condition 41.
11. Sapkal SB, Shelke KF, Shingate BB, Shingare MS (2009) Nickel nanoparticle-catalyzed facile and efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation under solvent-free conditions. Tetrahedron Lett 50: 1754-1756.
12. Shinde PV, Sonar SS, Shingate BB, Shingare MS (2010) Boric acid catalyzed convenient synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in aqueous media. Tetrahedron Lett 51: 1309-1312.
13. Shinde PV, Labade VB, Shingate BB, Shingare MS (2011) Application of unmodified microporous molecular sieves for the synthesis of polyfunctionalized pyridine derivatives in water. J Mol Cat A: Chemical 336: 100-105.
14. Shinde PV, Labade VB, Gujar JB, Shingate BB, Shingare MS (2012) Bismuth triflate catalyzed solvent-free synthesis of 2,4,6-triaryl pyridines and an unexpected selective acetalization of tetrazolo[1,5-a]-quinoline-4-carbaldehydes. Tetrahedron Lett 53: 1523-1527.
15. Pratap UR, Jawale DV, Bhosle MR, Mane RA (2011) *Saccharomyces cerevisiae* catalyzed one-pot three component synthesis of 2,3-diaryl-4-thiazolidinones. Tetrahedron Lett 52: 1689-1691.