



Multicomponent synthesis of heterocyclic compounds

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Abstract:

Rapid and efficient, multicomponent domino reactions (MDRs) are a useful tool for the one-pot synthesis of flexible heterocycles with diverse and complicated structures. Reduced chemical waste, lower starting-material prices, and lower energy and labour requirements are all possible thanks to these reactions. Additionally, the time required for a response may be greatly reduced. The most up-to-date research on multicomponent domino reactions for constructing heterocyclic skeletons with five, six, or seven members, as well as their multicyclic derivatives, is discussed in this Review. In recent years, our group has developed innovative procedures based on the transition-metal-mediated intramolecular addition reaction of heteronucleophiles and stabilised carbon nucleophiles to inactivated alkenes and alkynes. We provide a brief overview of many recent synthetic uses of these novel methods in this paper. Multicomponent reactions involving Pd-mediated intramolecular cyclization followed by carbon-carbon bond formation are the focus here.

Keywords: Ceria nanoparticles; Multicomponent reactions; Heterocycles; Catalyst; Synthesis.

Introduction

For the fast creation of molecular variety and complexity, multicomponent reactions are potent tools. An example of a multicomponent process is a reaction in which more than two components are mixed; this allows for a highly modular and efficient approach to the synthesis of structurally varied molecular entities. The production of small-molecule compound libraries using multicomponent reactions (MCRs) is a valuable technique for structure-activity relationship (SAR) investigations. The capacity to further functionalize or change the scaffold generated by certain MCRs is crucial for investigating the scaffold's biological value. Many of these scaffolds have an unconventional structure that makes them well-suited for investigating biological targets that more conventional scaffoldings do not access. Anti-aging drugs are



required to combat illnesses including Alzheimer's, Parkinson's, diabetes, and cancer, and novel scaffolds are in high need as drug-resistant organisms proliferate. Even if MCRs aren't solely responsible for developing medications to cure these illnesses in the future, they will undoubtedly play a role in the quest to find these treatments. The Strecker reactions are an example of a classic MCR. Reactions involving isocyanides, such as the Passerini reaction and the Ugi reaction, constitute the backbone of modern MCR chemistry. In this article, we will take a look back at the chemistry of isocyanides, with a focus on the process of nitrilium trapping.

Organic synthesis has been a major factor in the advancement of chemistry and has made important strides in resolving a number of the scientific problems that confront modern civilization. "In many sectors, such as pharmaceutical chemistry, the ability to manufacture new chemical entities in a planned and efficient way is essential, and this is becoming more true in fields like chemical biology and materials science. With the breadth of the chemical universe and the potential use of tiny molecules as probes in these areas, it is imperative that better synthetic techniques be developed. While considerable research effort is still directed toward traditional concerns like selectivity, molecular complexity, and synthetic efficiency, new aspects (such as sustainability, diversity-oriented synthesis, etc.) must be investigated to suit modern demands. Multicomponent reactions (MCRs) are highly valued in contemporary organic synthesis because they enable the coupling of three or more starting components to produce an adduct in a single step, resulting in both great atom economy and bond-forming efficiency. When assembling compound libraries, step economy is of the utmost importance because of the often-required brevity of the synthetic sequences. In addition to the MCRs' obvious benefits, our understanding of chemistry stands to gain from research into the dynamics of such complex systems and the engineering of the resulting domino effects. Contrarily, heterocycles are the most prevalent structural motif in bioactive chemicals and pharmaceuticals and hence are a favoured substructure. So, one of the primary aims of medicinal chemistry is the simple production of these molecules. The heterocyclic moiety may be included into the final adduct since MCRs have historically considered heterocycles either as the products (as in the conventional MCRs) or as the substituents of reactive functional groups. The direct use of heterocycles as reagents in MCRs is a third (complementary and more flexible) option. Using this modular strategy, novel drug-like scaffolds containing heterocyclic motifs may be created, capitalising on the abundant heterocyclic reactivity". In addition, it

facilitates the investigation of reaction channels in such systems. In this article, we give a selection of study findings that are illustrative of the power of this approach.

Review of literature

(Banik 2012) studied “Synthesis of Heterocycles Through Classical Ugi and Passerini Reactions Followed by Secondary Transformations Involving One or Two Additional Functional Groups Luca determined, and Many nitrogen-containing heterocycles can be easily synthesised in as few as one or two synthetic steps by combining classical isocyanide-based multicomponent reactions (Ugi and Passerini) with a variety of post-condensation transformations that take advantage of suitably positioned additional functional groups. To far, there have been several implementations of this tactic, all of which will be discussed in this article (September 2009). Particularly well adapted to combinatorial chemistry are the Passerini-named classical isocyanide-based multicomponent reactions (IMCRs), which enable the inclusion of three or four diversity inputs in a single synthetic phase. The widespread use of these methods in the creation of drug candidate libraries attests to their value.

(Haji 2016) studied Multicomponent reactions: A simple and efficient route to heterocyclic phosphonates discovered that and MCRs are one of the key procedures in the synthesis of highly functionalized organic molecules nowadays. This review shows their significance in organophosphorus chemistry, where phosphorus reagents are substrates for the production of various phosphorylated heterocycles.

(Váradí et al. 2016) studied Isocyanide-Based Multicomponent Reactions for the Synthesis of Heterocycles Found that and Multicomponent reactions (MCRs) are very well-liked because they are simple to carry out, produce a wide variety of products, and use few atoms. MCRs have shown to be important in the fields of total synthesis, drug discovery, and bioconjugation due to their ability to provide access to a wide range of heterocycles and highly functionalized scaffolds.

(Hügel 2009) studied “Microwave Multicomponent Synthesis” determined, and Multicomponent reactions are becoming more essential since they allow for the more efficient and ecologically friendly synthesis of multifunctional/complex target molecules, much as the way that extremely important research is typically undertaken by multidisciplinary research teams. In this article, we'll take a look back over the previous five years to examine the benefits and developments of microwave multicomponent synthesis (MMS). It is becoming more clear, from both an environmental and economic point of view, that the current approaches of

chemical synthesis are unsustainable and must be revised. Because they are more productive, economical, and resource-conserving than conventional approaches, multicomponent coupling reactions provide a viable alternative. Making many bonds in a multicomponent coupling process using a single pot is a step toward a more environmentally friendly synthetic method of discovering new molecules.

(Isambert et al. 2011) studied “Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis determined, and Today, it is possible to evaluate the efficacy of a chemical synthesis not only in terms of selectivity and overall yield, but also in terms of the amount of starting materials, the amount of time and labour required, the amount of energy consumed, the potential for chemical and protocol-related hazards, and so on.

(Isambert and Lavilla 2008) studied Heterocycles as Key Substrates in Multicomponent Reactions: The Fast Lane towards Molecular Complexity discovered that Heterocycles have a high level of inherent reactivity, making it possible to undergo complex, multipurpose, and fruitful transformations. Since these structures are so prevalent in pharmaceuticals and natural remedies, it is crucial that novel, rapid, and efficient preparative methods be developed for them. Taking use of this unique reactivity is made easier by multicomponent reactions using heterocyclic chemistry.

(Jiang et al. 2010) studied Multicomponent Reactions for the Synthesis of Heterocycles” Found that Multicomponent domino reactions (MDRs) are a useful tool for the one-pot synthesis of diverse heterocycles with complicated structures. These reactions have the potential to drastically cut down on chemical waste, initial material prices, energy consumption, and labour requirements. It's also possible to drastically cut down on the time required for reactions to occur. This Review summarises recent progress made in developing multicomponent domino reactions for constructing heterocyclic skeletons with 5, 6, and 7 members, as well as their multicyclic derivatives.

(Balme, Bouyssi, and Monteiro 2006) studied “Palladium-mediated cascade or multicomponent reactions: A new route to carbo- and heterocyclic compounds” determined, and We have developed novel methods in recent years that rely on the intramolecular addition reaction of heteronucleophiles and stabilised carbon nucleophiles to unactivated alkenes and alkynes, which is mediated by transition metals. Several recent synthetic uses of these novel methods are summarised in this article.

(Gore and Rajput 2013) studied “A review on recent progress in multicomponent reactions of pyrimidine synthesis Has been discovered that, and The multicomponent reactions (MCRs) are developing as environmentally benign synthetic techniques of building-up of complex molecules with maximal complexity and numerous levels of structural diversity for varied applications.

The Passerini–Ugi (P&U) classical isocyanide–based multicomponent reactions (IMCRs; Fig. 1) are ideal for combinatorial chemistry because they provide the simultaneous insertion of three or four diversity inputs. The widespread use of these methods in the synthesis of drug candidate libraries attests to their utility. Passerini and Ugi reactions in their traditional forms are ideal for investigating the variety of possible substituents, but are not useful for creating new scaffolds or heterocyclic systems. The latter disadvantage is significant because of the central role of heterocycles in medicinal chemistry, and numerous recent attempts have been made to address it. Even though they sacrifice one diversity input, intramolecular variations provide a valuable opportunity to explore heterocyclic systems. However, combining post-condensation transformations with the Ugi and Passerini reactions has shown to be the most effective technique.

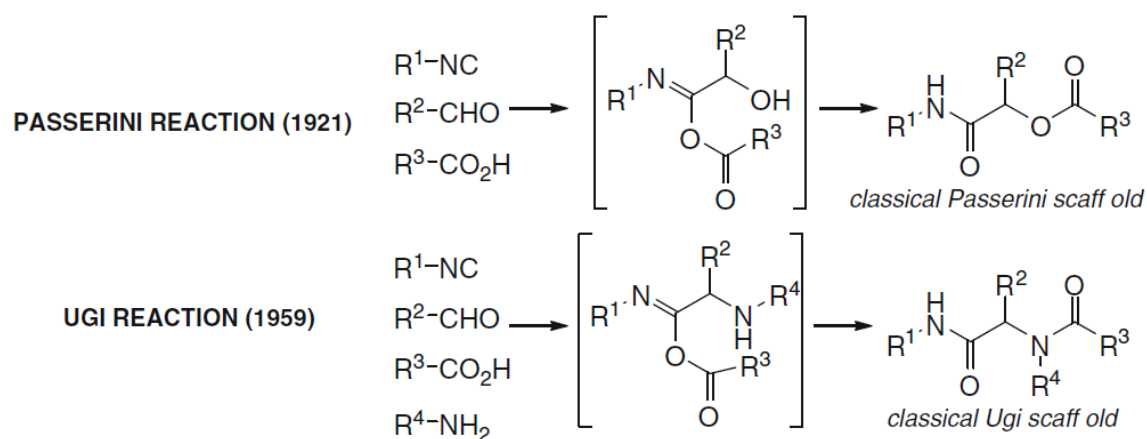


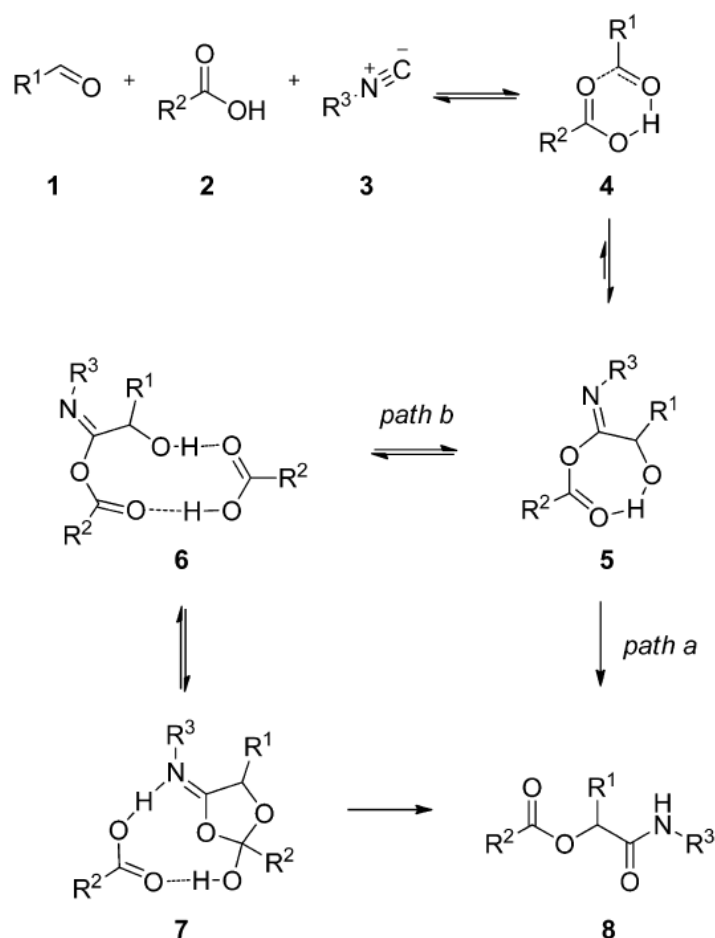
Fig. 1 Classical Passerini and Ugi reactions

MULTICOMPONENT REACTIONS WITH HETEROCYCLIC SUBSTRATES

Passerini Reactions

Isocyanide-based MCRs are unique among MCRs because of their ability to generate complex products from relatively simple reactants such aldehydes, ketones, carboxylic acids, and their

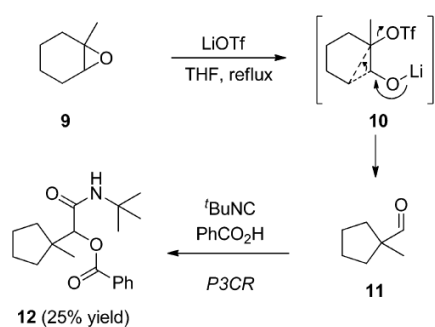
derivatives, and amines. The 1,1-amphoteric nature of the isocyanide functional group allows for the development of isocyanide-based MCRs. Two of the most well-known MCRs include isocyanides; these are the Passerini and Ugi reactions. To create α -acyloxycarboxamides, the Passerini method utilises a three-component reaction (3CR) using oxo compounds (1), carboxylic acids (2), and isocyanides (3). (8). To stimulate addition of the isocyanide, it has been proposed that a hydrogen-bonded cluster of the aldehyde and carboxylic acid (4) plays a role (Scheme 1). Whether or whether an isonitrilium ion forms as a separate entity is unknown.



Scheme 1. Proposed Mechanisms of the Passerini Reaction As Described by Maeda et al.2

The α -addition is a collaborative effort. Multiple possible paths have been proposed by computational studies, and it is probable that some of them are active depending on the reaction circumstances (Scheme 1).² The α -addition is probably irreversible, and the transacylative collapse of a mixed anhydride is the thermodynamic driving force.

Substituting a tiny heterocycle for one of the components of a known MCR is one way to increase the MCR's reactive range. An MCR involving an epoxide, a carboxylic acid, and an isocyanide was established by Kern and Motherwell as a modification of the Passerini reaction; an epoxide was employed as the initiating electrophile rather than an aldehyde.³ This reaction required a metal triflate catalyst. For instance, 1-methylcyclohexene oxide (9) was converted to 1-methylcyclopentane-1-carboxaldehyde (11) by the skeletal rearrangement⁴ of 1-methylcyclohexene oxide (9) to 1-methylcyclopentane-1-carboxylic acid (12) using an isocyanide and carboxylic acid in a classic Passerini reaction (Scheme 2)".



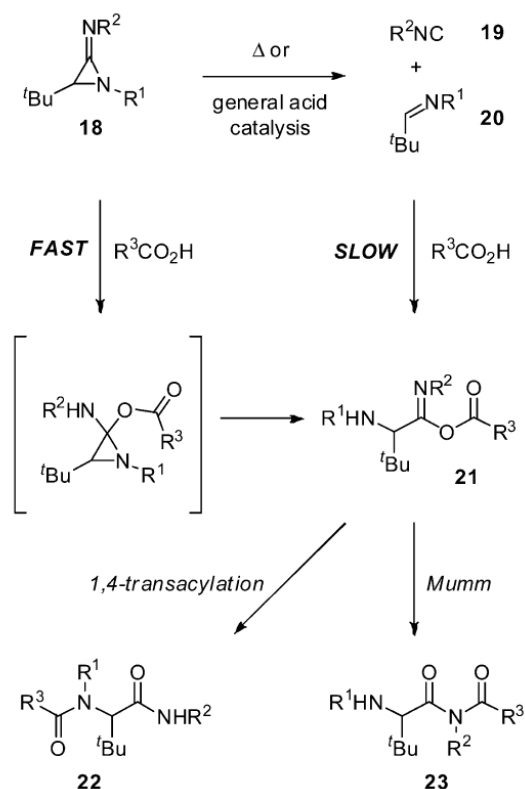
Scheme 2. Rearrangement of 1-Methylcyclohexene Oxide (9) to 1-Methylcyclopentane-1-carboxaldehyde (11) Prior to P3CR

Ugi Reactions

Ammonia or a primary or secondary amine are added to the Passerini reaction, resulting in the 4CR known as the Ugi reaction.⁶ "The electrophilic iminium ion is formed during the condensation of the amine and oxo components, and it combines with the isocyanide and carboxylate with remarkable selectivity compared to the potentially competing P3CR. The ensuing mixed anhydride intermediate readily undergoes transacylative breakdown to provide -acylaminoamides. Attempts to understand the underlying processes of the Ugi reaction via computational modelling have shown that the kind of solvent used may lead to slight but significant alterations in the reaction's fundamental phases.⁷ Protic solvents are the norm for the U4CR (Ugi fourcomponent reaction),⁸ and an isonitrilium intermediate was discovered in theoretical investigations using a methanol solvent model, in contrast to the P3CR. According to current thinking, the isocyanide reaction is rate-determining in all solvents. The amide formation provides the thermodynamic impetus. Iminoaziridines (18) serve as synthetic precursors for three components of the U4CR, just as epoxides do for the Passerini reaction's oxo component. Isocyanide 19 and imine 20 are formed when 18 undergoes heat activation or



general acid catalysis. The U4CR reaction then continues when a carboxylic acid is present. The identical mixed anhydride intermediate (21) and related rearrangement products are produced by direct addition of a carboxylic acid to 18 at low temperature (Scheme 4).⁹ Using sterically hindered carboxylic acids like di-tertbutylacetic acid, highly reactive iminoaziridines enabled for the characterisation of 21 in solution by ¹H and ¹³C NMR. In contrast, production of 21 is the rate-limiting step in the U4CR. This research revealed a number of interesting facts. It was found that nonracemic iminoaziridines (18) produced hardly any racemized products.



Scheme 4. Iminoaziridines (18) Provide an Alternative Approach to the U4CR

The absence of intermediates 19 and 20 implies that the reaction does not occur through a retro-[2 + 1] cycloaddition. Instead, the sterically hindered carboxylic acids (such as ditert-butylacetic acid) readily combine with 18 to form nonracemic Ugi products that are useful in synthetic chemistry (22). Formation of 22 via 1,4-transacylation was preferred less than the 1,3-Mumm rearrangement, which yielded imide 23, when the aziridinylnonsubstituent was big (i.e., R1 = tBu, Scheme 4). If the reaction was heated or given too much carboxylic acid, the selectivity swung in favour of 22, although this had no effect on the reaction's stereochemistry. Given the past difficulties in creating asymmetric Ugi reactions, this is of paramount importance".¹⁰

Conclusions

The most up-to-date sources and procedures for the synthesis of a wide range of pyrimidine derivatives using modern-day MCRs are presented. The catalyst systems for the synthesis of pyrimidines are not discussed, but the development of solvent systems from non-aqueous to aqueous and solvent-free is described. If you're just getting started learning about the synthesis of the physiologically significant pyrimidine scaffold, this brief overview should be a great

resource. Due to their atom-economy and green chemistry features, MDRs have become more significant for the production of chemically and medicinally valuable molecules. These reactions allow for the simultaneous completion of many steps in a single operation, resulting in a wide range of valuable, structurally complicated heterocyclic compounds. MDRs may drastically cut down on chemical waste and initial material costs as compared to conventional multi operational synthesis.

An energetic property of one or more reactants provides the impetus for a multicomponent reaction. Opportunities for atom-economical synthesis of organic compounds are available through multicomponent reactions involving tiny ring heterocycles, which are driven by strain release. Notably, other causes might also give the impetus, leading to

potentials for tiny heterocyclic molecule product structures to be preserved in their essential forms. More chances for site-selective structural alteration exist thanks to the preservation of strained rings in the products, as described in many of the examples discussed in this paper. Sometimes, multicomponent synthesis will even allow for the construction of tiny ring heterocycles. According to our trend analysis, new instances of cascade and multicomponent reactions are most likely to be uncovered by either investigating transition-metal catalysis or by developing new densely functionalized building blocks.

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