Review on the Ugi Multicomponent Reaction Mechanism and the Use of Fluorescent Derivatives as Functional Chromophores

Rafael O. Rocha,† Marcelo O. Rodrigues,‡* and Brenno A. D. Neto*†

†Laboratory of Medicinal and Technological Chemistry, University of Brasilia, Chemistry Institute (IQ-UnB), Campus Universitário Darcy Ribeiro, Brasilia, Distrito Federal 70904-970, Brazil
‡School of Physics and Astronomy, Nottingham University, NG72RD Nottingham, U.K.

ABSTRACT: In the present mini-review we discuss the findings, controversies, and gaps observed for the Ugi four-component reaction. The Ugi multicomponent reaction, performed by mixing an aldehyde, an amine, a carboxylic acid, and an isocyanide, is among the most important isocyanide-based multicomponent reactions (MCRs), allowing multiple bond formations (C−C and C−N) in a single synthetic step. The possibility of two reaction pathways and the little understood solvent effect over this transformation renders this reaction as one of the hardest challenges to overcome. The little knowledge of the mechanism of the Ugi MCR hinders the development of new and efficient chiral catalytic systems to further the application of the derivatives obtained by enantioselective versions. The asymmetric transformation is in this context a bigger challenge, and little is known about the mechanism of these few available versions. The new trend of functional chromophore synthesis by MCRs is also highlighted, and the few examples already disclosed in the literature exemplify the huge opportunity for investigation and creative ideas using the Ugi four-component reaction.

INTRODUCTION

The Ugi multicomponent reaction (MCR) is the eponymous of a four-component transformation disclosed in 1959 by Ivar Ugi.1 This important transformation belongs to the class of the so-called isocyanide-based MCRs and demands the use of an aldehyde, an amine, an isocyanide, and a carboxylic acid to take place and affords an α-acetoamido carboxamide derivative (Scheme 1). The Ugi adducts are sometimes referred to as peptoids. The large number of available publications describing different features, conditions, catalysts, effects, diversity-oriented syntheses, and application of such MCR adducts leaves no doubt of both the importance and the feasibility of the reaction as a synthetic tool available in the modern Organic Chemistry toolbox.

Although the Ugi MCR is largely studied in relation to its synthetic application and diversity-oriented syntheses, there is plenty of room in terms of mechanistic investigations and in the design (and synthesis) of new fluorescent derivatives, as we intend to critically show herein. One may indeed conclude that little knowledge is available to support the development of new catalysts and to control the enantioselectivity (or diastereoselectivity) of this tricky transformation.

The possibility of more than one reaction mechanistic pathway operating at the same time in a concurrent manner renders the attempts to decipher the key parameters to control this MCR as a highly complex challenge, especially to reach a rationale for the chiral induction step of enantio- and diastereoselective versions.

Many applications are noted in the current literature related to the Ugi MCR. A recent and important trend is the synthesis of functional chromophores using MCRs.2 Fluorescent Ugi adduct derivatives have been barely explored. As will be shown herein, only a few examples have been described exploring the “photo” properties of these molecules. There are almost no reports of the use of these fluorescent derivatives as bioimaging probes.

In the current mini-review, we intend to show the readers state-of-the-art information regarding the mechanistic knowledge and what is currently under debate. A separated section will discuss the enantioselective version of the Ugi MCR and
the available mechanistic evidence. The application of fluorescent derivatives focusing on their design and emission properties will be also analyzed and disclosed herein. Variations of the Ugi MCR (reviewed elsewhere) are outside the scope of this manuscript, and these articles will be cited only as exceptions.

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**UGI MULTICOMPONENT REACTION MECHANISMS**

As is usual for MCRs, it has been proposed that there is more than one reaction pathway for the Ugi transformation. MCRs typically have two (or more) reaction pathways occurring at the same time; however, they are also usually convergent, and the final adduct may be formed through different reaction pathways. The conditions to select one mechanism instead of the others are however still unclear for most of the MCRs. Today, the current understanding is that the Ugi four-component reaction may proceed through two competitive reaction pathways, as seen in Scheme 2.

The solvent choice to conduct the Ugi reaction has some contrasting reports. Polar and protic solvents (e.g., methanol, ethanol, or trifluoroethanol) are the common preference for the Ugi 4-CR, but polar aprotic solvents (THF, DMF, dioxane, or dichloromethane) may also return good results in some specific reactions. For some cases, aqueous media may also be used with relative success. The preferences for protic solvents rely on the fact that the intermediates noted in the general mechanisms (Scheme 2) are polar derivatives (prone to H-bond formation) that are consequently stabilized in these solvents. The proton transfer TS (see Scheme 2) may aid the understanding of this preference. Aprotic solvents may help in the stabilization of the proposed TS, despite the fact that the formation of the first key intermediate (i.e., imine or iminium ion in Scheme 2) may be favored in polar and protic solvents.

Despite the fact that there are disputes about the current preferred reaction pathway of the Ugi reaction, some features were widely accepted, i.e., the imine (or the iminium) formation as the first intermediate. This intermediate plays a key role in conducting the reaction toward the final adduct, as we have shown. Two possibilities are however viable, that is, the isocyanide addition (classical view) affording the nitrilium ion or the carboxylic acid insertion, as proposed a few years ago, leading to the hemiaminal intermediate (Scheme 3). Both proposals converge to the imidate intermediate, which in turn undergoes the Mumm rearrangement and affords the final Ugi adduct.

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**Scheme 2. Current Two Debated General Reaction Pathways Observed for the Ugi Multicomponent (Four-Component) Reaction**

Although the classical view of the Ugi reaction mechanism was accepted until it was challenged by the breakthrough report of Fleurat-Lessard and co-workers, a systematic evaluation was only reported a few years ago by our group. In the work, we disclosed a systematic investigation of the Ugi four-component reaction by ESI-MS(/MS) and applying the charge tag strategy for MS mechanistic investigations using imidazolium derivative reagents (Scheme 4). The strategy allowed for the detection and characterization of key intermediates and pointed firmly to the preference of the classical view of the reaction with the formation of the nitrilium ion (Scheme 3). In the experiment, no intermediate of the hemiaminal pathway could be observed.

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**Scheme 3. Competitive Mechanisms from the Iminium Ion**

**Scheme 4. Charge-Tagged Reagents, Detected and Characterized Intermediates, and Side Reaction of the Ugi Four-Component Reaction Evaluated by ESI-MS(/MS)**
The use of the charge-tagged reagents allowed for the detection and characterization of the key iminium (or imine) intermediate of m/z 138 and of m/z 120 using the charge-tagged reagent and the ordinary reagent, respectively. Before the detection of this intermediate, no other intermediates were noted, and this pointed to the importance of this mechanistic step which is usually not pointed out as the rate-limiting step. The important nitrilium ion intermediate detection (m/z 221) was possible due to the presence of the charge-tagged amine derivative in its structure. The final Ugi adduct (m/z 343) could be also detected and characterized using the charge-tagged acid derivative. Although there were efforts to characterize the intermediate before the Mumm rearrangement (i.e., imidate), its detection and characterization was not possible.

The characterization of the imidate ion, a key intermediate formed prior to the Mumm rearrangement (Scheme 2), was important to a full characterization of the mechanism evoked for the Ugi MCR. This step was found to be strongly exothermic in nature, and the Ugi reaction was likely driven by the thermodynamics associated with this last transformation, as noted elsewhere. The solvent also has an important influence over the energetic barrier is higher than when two molecules were computed. The basis for this work was found in a previously reported study, where the MS data pointed to the idea of a reversible Mumm rearrangement (Scheme 6). The set of techniques applied to characterize the imidate structure revealed that the energetic barrier is higher than when two molecules were computed. Similar results were computed when Ugi–Smiles was investigated in the same work. The presented established view on the Ugi reaction mechanism, with the iminium (or imine) intermediate as the splitting point (see Scheme 3), has been however questioned a few years ago. Instead of the isocyanide addition to this intermediate, the possibility of the carboxylic acid insertion to afford the hemiaminal intermediate has been proposed. Comparable insertions may be found when isocyanide chemistry is evaluated, but the detailed theoretical study disclosed elsewhere revealed the crucial role of H-bonds (between the imine intermediate and the carboxylic acid) to activate the imine structure to shift the reaction toward the imidate intermediate (Scheme 7), which in turn undergoes the Mumm rearrangement. Similar results were computed when methanol was used as the explicit solvent, but the energetic barrier is higher than when two molecules were computed.

Later, it was found that the reagents’ structures may also play a role in the reaction pathway selection, but the hemiaminal intermediate (see Scheme 3) was not detected at all, even when benzoic acid was used in large excess in a solution containing the preformed iminium ion aiming at forcing this intermediate formation to further MS(/MS) detection and characterization. Based on the obtained results, the authors suggested this mechanism should be definitely rejected. These results proved to be in accordance with the results previously published by some of us. Some theoretical results also pointed to the isocyanide addition affording the nitrilium intermediate as the rate-determining step of the Ugi MCR.
ENANTIOSELECTIVE UGI MULTICOMPONENT REACTION MECHANISM

The challenge for effective chiral induction and control in MCRs is huge, as we have recently highlighted. The development of efficient methodologies is intimately associated with both the comprehension of the mechanism of a specific reaction and the way to tune the parameters (solvent, temperature, etc.) to further the transformation.

The Ugi MCR has been recently labeled as "unconquered" regarding an effective enantioselective version, meaning there is much room for improvement in this field of research. Mechanistic studies with convincing experimental and theoretical data, of enantioselective MCRs, are rarely found in the scientific literature, but there are a few exceptions, as we have recently published. A breakthrough work in this field has been recently reported by Zhang and co-workers evaluating the enantioselective Ugi MCR using asymmetric phosphoric acid derivatives as catalysts (Scheme 9).

In the work, some chemical tests were conducted to get insights into the reaction mechanism and the role of the catalysts in the enantioselective Ugi MCR. Using amine excess (2 equiv; see Scheme 9), the reaction did not proceed. It pointed out an important feature of the catalyst action, implying the chiral phosphoric acid itself was responsible to promote the reaction. It meant no phosphate-conjugated base or any other deprotonated derivative was involved in the transformation. The early imine (iminium) formation was found to be as initially suggested by us, and similar results regarding yields and enantiomeric excesses have been noted in both the three- (using preformed imine) and four-component versions. A heterodimer, formed by treating the chiral phosphoric derivative with the carboxylic acid reagent, has been proposed to act as the species responsible for imine activation (Figure 1). Activation of carboxylic acids by heterodimerization with chiral phosphoric acids has already been proposed and explained elsewhere.

Scheme 7. Calculated Reaction Pathway of the Ugi Reaction Considering Methanol (Purple Values) and Toluene (Black Values) As Solvents

Scheme 8. Calculated Reaction Pathway of the Ugi Reaction Mumm Rearrangement Step Considering Two Explicit Methanol Molecules (Computed Solvent)

Scheme 9. Enantioselective Ugi Reaction Catalyzed by Chiral Phosphoric Acids
DFT calculations supported the proposed scenario and gave the grounds to understand the reaction outcomes using the chiral catalysts tested in their work. Based on the theoretical evaluation of the enantioselective Ugi MCR, a reaction mechanism and the involved energetics were depicted (Scheme 10). The importance of noncovalent interactions during the transition state to an efficient chiral transmission and to succeed the transformation was also highlighted. An in-depth analysis of the importance of noncovalent interactions, especially during the transition state of the chiral transmission step for enantioselective MCRs, may be found elsewhere.

In the past few years, MCRs have been used as a powerful tool for the generation of libraries of functional chromophores. Two distinct strategies applied in the synthesis of such functional chromophores are observed (Scheme 11) using MCRs: (i) the use of one of the reagents bearing a chromophoric framework (known as scaffold approach) or (ii) the MCR acts as a chromogenic event, and the final product displays the features of a chromogenic adduct (known as chromophore approach).

This strategy has been used, for instance, in the synthesis of 14 derivatives of donor–acceptor systems where the phenothiazine acts as the donor, whereas the 9,10-anthraquinone is the acceptor moiety (Scheme 12). The absorption characteristics of the synthesized compounds have been evaluated and showed similar behavior to a system lacking electronic communication with the acceptor moiety in the ground state. In the excited state a quenching could account for the fast electron transfer from the donor to the acceptor as depicted by femtosecond spectroscopy.

Fluorescent peptoids obtained from the Ugi four-component reaction have been synthesized (Scheme 13) using the scaffold approach (Figure 1) and applied as selective probes for bioimaging applications by our group. These four new derivatives shown in Scheme 13 had their photoproperties evaluated and their abilities as live cell...
fluorescence imaging probes verified. Derivative P4 had a strong affinity for mitochondria and could be used as a new selective blue emitter to stain these important organelles (Figure 2).

A close look in the literature will show the readers a few more examples of functional chromophore derivatives synthesized using the Ugi MCR applying the scaffold approach. This is a clear indication of the vast field to be explored in the next years by using these two approaches (Figure 1). Although the possibilities of photoapplication of these derivatives may be huge, the limited number of available works found in the scientific literature highlights that we are still crawling in this area and also shows a window of opportunities.

**CONCLUDING REMARKS**

The available knowledge of the Ugi four-component reaction is still very limited, and the most available data are based on the use of the ESI-MS(/MS) technique. Although the generated information was highly valuable and shed some important light on the comprehension of this truncated transformation, there is much to be done yet. Kinetic data for MCRs are a true challenge to be collected and analyzed, and no data are available for the Ugi four-component reaction. The current available reports indicate the preferential reaction pathway is through the nitrilium ion after the imine (or iminium) formation. The formation of the hemiaminal intermediate is still controversial, and its proper characterization is a gap to be filled. The imidate intermediate, formed immediately before...
the Mumm rearrangement, requires additional characterization, and most information available is because of the retro-Mumm reaction monitored by MS and IRMPD. Thus, it is fair to conclude we know so little about this MCR, and most of their mechanistic steps are urging for deep investigations and characterizations.

When the few enantioselective versions of the Ugi four-component reactions are considered, the lack of knowledge is enormous. Beyond the characterization of the preferred reaction pathway, it is important to understand the key step of the chiral transmission and to control the factors ruling this phase. Without this knowledge, the development of new and efficient catalytic systems is being hindered.

The few examples found in the literature showing the synthesis and application of functional fluorophores obtained by the Ugi MCR exemplify the vast field of opportunities available for new, creative, and innovative ideas. The "photo" field of technology has a lot of opportunities, and the development of Ugi adducts applying the two approaches (i.e., scaffold and chromophore) may allow for the improvement and tuning of absorption/emissive properties as well as biological responses, especially considering the large number of compounds which may be synthesized by this important MCR.

With this mini-review we hope to help readers to dive in this field of research, and we are looking forward to reading the new advances regarding the mechanistic elucidation and the photoapplication of the Ugi four-component reaction derivatives.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: brenno.ipi@gmail.com.

ORCID
Marcelo O. Rodrigues: 0000-0003-0684-3618
Brenno A. D. Neto: 0000-0003-3783-9283

Notes
The authors declare no competing financial interest.

Biographies
Brenno A. D. Neto’s research interests include the development of new catalytic systems, mechanistic investigations, multicomponent reactions, and applications of rationally designed selective fluorescent bioimaging probes. He has received some national and international awards, including the RSC/BMOS Young Investigator Award (2013), Honorable Mention for the Best Brazilian Thesis in Chemistry 2013 (Category: Advisor), Affiliated Member of the Brazilian Academy of Sciences (2014), and the Petrobras Inventor Award for the best patent filed in 2008. He has nearly 100 international publications reported only in traditional and respected Journals and more than 15 patents and has acted as advisor of many Graduate students.

Marcelo O. Rodrigues studied chemistry at the University Federal of Pernambuco. In 2011 he started the independent carrier at the University Federal of Pernambuco. Marcelo’s expertise lies in the new photoluminescent materials such as nanomaterials, metal–organic frameworks, ceramics, composites, and their application as technological materials such as for living cell imaging probes, forensic science, solar cells, and agriculture. His research has a multi-disciplinary character, and he has established cooperation in nanomedicine and pharmacy (nanoformulation against tegumentary leishmaniases), biology (nanoprobes for bioimaging), energy (luminescent persistent materials for solar cells applications), forensic science (luminescent gunshot residues), and agriculture (photosynthesis booster and nanobiostimulants for crop and microalgae). Marcelo is a co-founder of the startup Krilltech Sustainable Solutions.

Rafael O. Rocha received his degree in Chemistry from the University of Brasilia (UnB) in 2002. In 2007, he completed his Ph.D. at the same University. He has been a professor in the Institute of Chemistry at the University of Brasilia since 2008. His research interests include the development of new organocatalysts and their application in enantioselective organic reactions, multicomponent reactions (MCRs), mechanistic investigations, and new methods in organic chemistry, especially for different MCRs using isocyanides, and their applications in synthesis of natural products.

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