

Ugi Multicomponent Reaction Based Synthesis of Medium-Sized Rings

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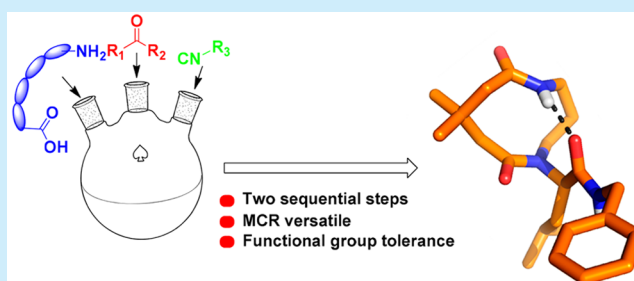
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S Supporting Information

ABSTRACT: An Ugi multicomponent reaction based two-step strategy was applied to generate medium-sized rings. In the first linear expansion phase, a series of diamines reacted with cyclic anhydrides to produce different lengths of terminal synthetic amino acids as the starting material for the second phase. The Ugi-4-center 3-component reaction was utilized to construct complex medium-sized rings (8–11) by the addition of isocyanides and oxo components. This method features mild conditions and a broad substrate scope.



Medium-sized rings are molecules which contain between 8 and 11 ring atoms.^{1,2} Surprisingly, they are highly underrepresented in screening libraries and in general in the synthetic organic chemistry world. Examples of bioactive medium-sized cycles, however, exist and include taxol (8-membered), griseoviridin (9-membered),³ crotalanian alkaloids (10-membered), and diplodialide natural products (11-membered).⁴ As opposed to small rings or macrocycles, medium-sized rings are a challenging class of synthetic targets.⁵ While small rings can often be closed based on favorable enthalpy, macrocyclic ring closure needs a favorable entropic component. Medium cycles, however, often show an unfavorable entropy and enthalpy component, including Pitzer ring strains and transannular interactions, for their ring closure and thus are highly demanding synthetic targets.⁶ Different synthetic methodologies have been applied for the ring closure of medium-sized cycles, including ring-closing metathesis (RCM), macro-lactonization, metal mediated C–C coupling reactions, and ring expansion.⁷ However, these methods mostly suffer from low yields and limited substrate scope. Therefore, the discovery of general methodologies for the fast and efficient construction of various medium rings in good yields and with useful levels of diversity is of considerable importance. Our design toward the synthesis of complex medium ring structures is based on two simple but diverse reactions steps. Moreover, it is based on commercially available starting materials. The first step involves a ring opening reaction of cyclic carboxylic acid anhydrides with unprotected diamines to afford α,ω -amino acids. In the next step, α,ω -amino acids are used in an Ugi reaction with oxo components and isocyanides to close medium rings of 8–11 membered size (Figure 1). This method closely follows our recently described strategy to create a

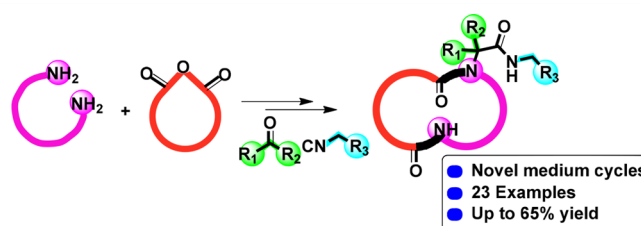


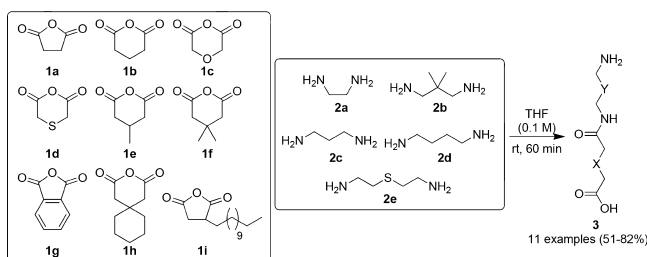
Figure 1. Described macrocyclization strategy.

manifold of artificial macrocycles by a short sequence involving an initial linear diversification, followed by an exponential diversification step of macrocyclization using an Ugi and Passerini multicomponent reaction (MCR).^{8,9}

We initially started our study by the synthesis of α -amino ω -carboxylic acid by reacting symmetrical and unsymmetrical cyclic anhydride with diamines followed by an Ugi reaction. We reacted a total of nine cyclic anhydrides with five diamines providing 11 amino acids of different linker length (Scheme 1).

For the synthesis of medium-sized ring compounds, we focused on the small diamines, such as ethylene diamine, propane diamine, butane diamine, and pentane diamine derivatives (Scheme 1). The ring opening reaction of cyclic anhydrides was carried out by slowly dropping anhydride to the unprotected alkyl diamine solution in THF as an aprotic polar solvent. This reaction proceeded under diluted conditions (0.1 M), on a 10 mmol scale, at room temperature, and the product α -amino ω -carboxylic acid was isolated in good yields (59–80%). Next, the macrocyclic ring closure was performed by Ugi

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Scheme 1. Starting Materials for the Synthesis of α -Amino ω -Carboxylic Acids^a

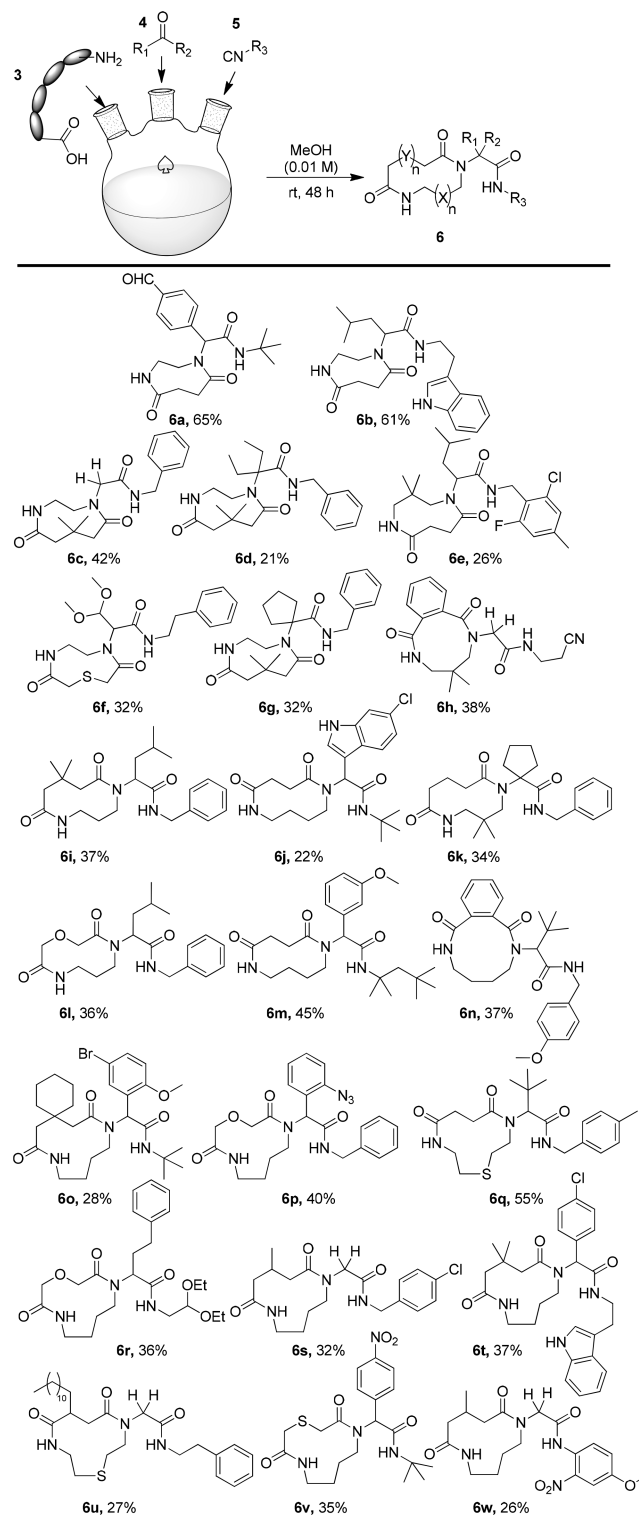
^aAll starting materials are commercially available.

MCR under optimized conditions using 1 equiv of oxo component and isocyanide (Scheme 1). We extensively screened different conditions by varying temperature, solvent, and time. By using methanol as a solvent at 0.01 M concentrations of reactants and after 48 h at room temperature, a range of medium-sized rings were obtained in optimal yields. To investigate substrate scope and limitations, we synthesized 23 examples, as shown in Scheme 2. Several commercially available aliphatic, aromatic, and heteroaromatic aldehyde and ketone building blocks reacted as oxo-components in the Ugi reaction to afford the medium-sized cycles in acceptable good to excellent (21–65%) yields after purification by column chromatography. Various functionalized isocyanides, such as aliphatic, aromatic, and benzylic, including indole-derived isocyanides, reacted well to give the desired products.

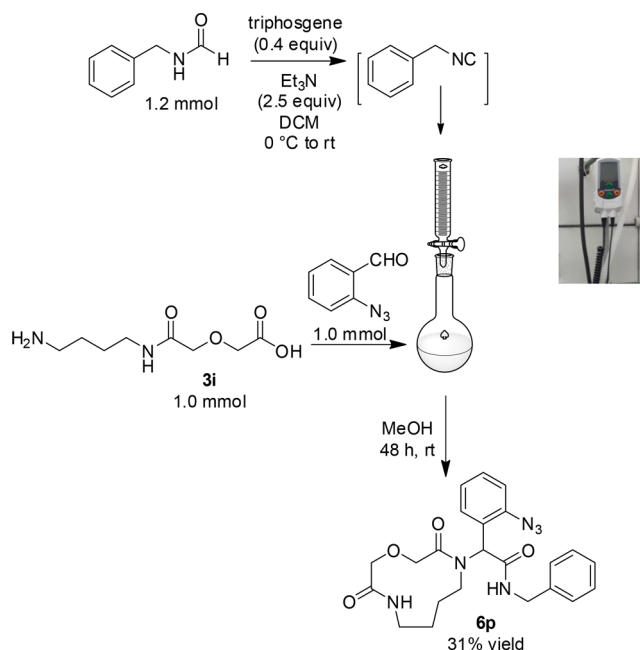
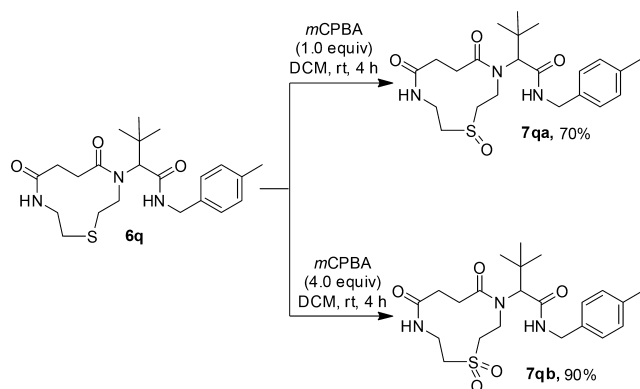
In light of our efforts to find an effective method of synthesizing medium-sized rings in a one-pot reaction, including amino acid synthesis and also *in situ* isocyanide synthesis, we used some unpurified synthetic amino acids in the ring closure step by simply removing the THF solvent from the anhydride ring opening reaction and reacting the crude amino acid with the oxo and isocyanide components in methanol. With this one-pot procedure, we were able to produce medium-sized rings (for examples, 6a, 6b, 6h, 6k, and 6u) in 27% to 65% yields. In a similar way, we also simplified and extensively studied the *in situ* isocyanide formation and ring closure reactions in one pot. Thus, we used our recently described *in situ* isocyanide synthesis protocol from formamides to produce the complex IMCR products in one pot, without tedious synthesis and isolation of the foul smelling and toxic isocyanides.¹⁰ Triphosgene (0.4 equiv) with Et₃N (2.4 equiv) in dichloromethane (DCM) (0.5 M) proved to be the best dehydrating system for the isocyanide formation. *N*-Benzylformamide was treated with 2.4 equiv of Et₃N and 0.4 equiv of triphosgene in DCM (0.5 M) as solvent at 0 °C. After 15 min, the crude mixture was passed through a small bed of silica gel into a round-bottom flask, which already contained amino acid 3i and 2-azidobenzaldehyde, as shown in Scheme 3. The reaction mixture was stirred for another 48 h, and the 11-membered medium-sized ring product (6p) was obtained in 31% yield after column purification. These *in situ* methods will increase the value of MCR chemistry, even though the *in situ* isocyanide process gives a lower yield compared to the procedure involving isolation and purification of the isocyanide and amino acid (6p, 40% yield, Scheme 3).

A determinant of passive membrane permeation is the potential of macro- and medium-sized cycles to form intramolecular hydrogen bonds which improve their chameleonic behavior by switching between conformations in

Scheme 2. Ugi-4CR Synthesis of Medium-Sized Rings and the Product Structures with Isolated Yields

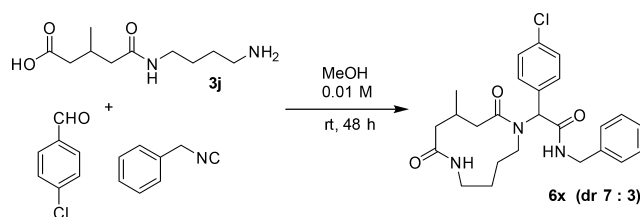


aqueous solution and while passing through lipid cell membranes by exposing polar atoms and hydrophobic residues, respectively.¹¹ Thus, we were interested in oxidizing the sulfur medium-sized cycle 6q to the sulfoxide and the sulfone, respectively. The chemistry to the sulfoxide and sulfones was accomplished by *m*-chloroperbenzoic acid (*m*CPBA) in DCM (Scheme 4). The compound 6q was reacted with 1.0 and 4.0 equiv of *m*CPBA in DCM for 4 h to afford sulfoxide 7qa and

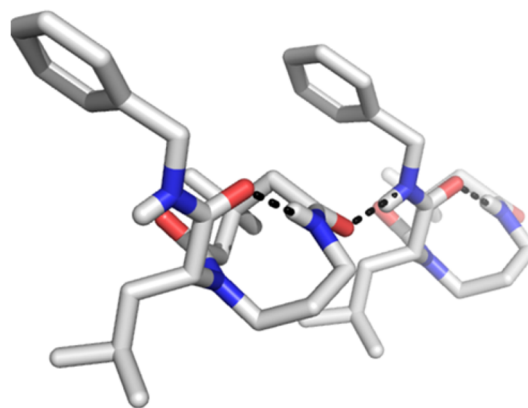
Scheme 3. One-Pot *in Situ* Isocyanide Synthesis Followed by Ugi-MCR**Scheme 4. Selective Oxidative Modifications on Refractory Sulfur Contained Medium Cycles**

sulfone **7qb** in excellent yields (70% and 90%, respectively). Our future plan is to investigate how this sulfoxide and sulfone can participate in the formation of amide–sulfoxide and amide–sulfone intramolecular hydrogen bonds and thus determine the 3D conformations.

Diastereomer formation was also investigated by reacting **3j**, chlorobenzaldehyde, and benzyl isocyanide. Not surprisingly, a moderate dr of 7:3 was observed by ^1H NMR of the crude reaction mixture (Scheme 5).

Scheme 5. Example of Reaction Diastereoselectivity

In order to confirm the product structure and to gain insight into the ring conformation and intra- vs intermolecular hydrogen bonding, we crystallized compound **6i** and determined its solid-state structure by X-ray crystallography (Figure 2). Interestingly, in the **6i** structure, the exocyclic

**Figure 2. Representative MCR-derived 10-membered ring **6i** in solid state featuring intramolecular and intermolecular hydrogen bonding contacts.**

isocyanide derived amide group is bending back over the macrocycle to form an intramolecular hydrogen bonding with the medium-sized cycle amide group. Moreover, the medium cycle secondary amide undergoes a hydrogen bonding with the same amide group of a neighboring medium cycle. This kind of intramolecular hydrogen bonding in related medium or macrocyclic systems has been determined to facilitate passive membrane diffusion, an important determinant of cellular activity and oral bioavailability.^{12,13}

Physicochemical properties are of uttermost importance for the usefulness of compounds as chemical probes or development candidates. What is the profile of our medium-sized cycles? To answer this question, we constructed a random virtual 1000 medium ring library (Supporting Information). Then, we calculated the properties of the library, including molecular weight, lipophilicity, number of hydrogen bond donors and acceptors, number of rotatable bonds, polar surface area, and moment of inertia. Interestingly, an analysis of the library shows 30% obey the Lipinski rule of five (ROS). Even more stringent central nervous system multiparameter optimization (CNS MPO) desirability can be reached for a percentage of the compound.¹⁴ The cLogP versus MW distribution is favorably drug-like with an average MW and cLogP of 538 and 3.3, respectively (Figure 3). Moreover, punctual analysis of 3D modeled representatives and X-ray structures underline the nonflat shapes of the medium-sized rings.

In conclusion, we introduced a very mild, straightforward two-step, rapid, and highly diverse medium-sized cycle (8–11 membered) synthesis pathway via MCRs. The strategy using an Ugi reaction in the cyclization is particularly appealing for several reasons. First, it offers outstanding diversity. Second, it potentially provides various medically and pharmaceutically important products containing an amide bond that can serve as conformationally constrained peptidomimetics. Finally, this strategy will allow a unique route for the synthesis of medium-sized cyclic nonpeptidic molecules. We are currently synthesiz-

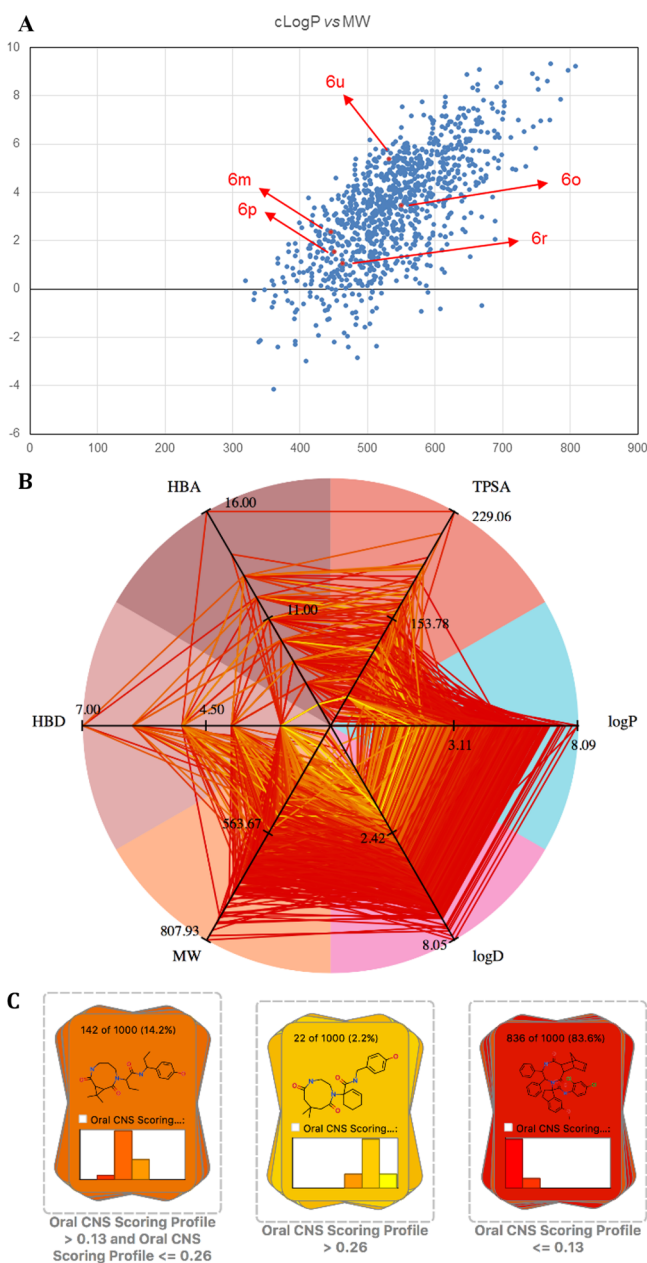


Figure 3. Some calculated physicochemical properties of the chemical space of medium-sized rings. (A) cLogP over MW scatter plot. (B) Oral CNS scoring radar plot. (C) Compound distribution based on oral CNS scoring.¹⁴

ing and screening extensive medium-ring libraries and will report on their biological activity in due course.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs-orglett.7b03094.

General procedures, characterization data of all the compounds, crystal structure determination and computational chemistry (PDF)

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Notes

The authors declare no competing financial interest.

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