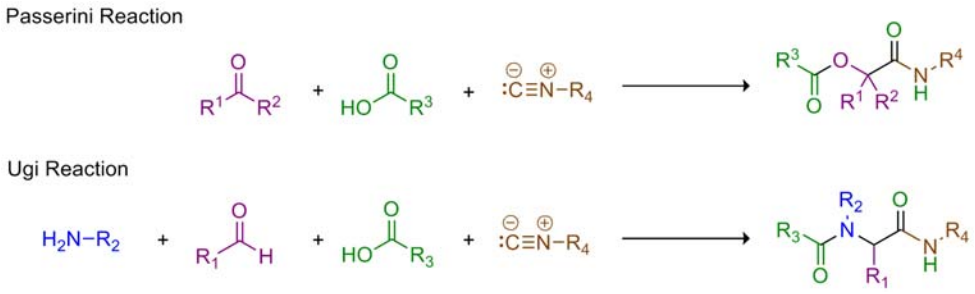
The Ugi Multicomponent Reaction: Stereocontrol, Modifications and Applications

Reported by Stacie Lynn Richardson February 19, 2007

INTRODUCTION

The Ugi reaction was first reported by Ivar Ugi in 1959.[1] Along with the Passerini reaction, it is classified as an isocyanide-based multicomponent reaction.[2] The prototypical reaction (**Scheme 1**) results in the formation of an α-*N*-acylamino amide. The reaction is usually conducted in a polar protic solvent such as methanol, and some success in water has recently been shown.[3] Usually, non-polar halogenated solvents prove detrimental, as most amines are insoluble, favoring the occurrence of the Passerini reaction.[4] The mild reaction conditions allow for inclusion of a variety of functionality.

Scheme 1. Passerini and Ugi reactions



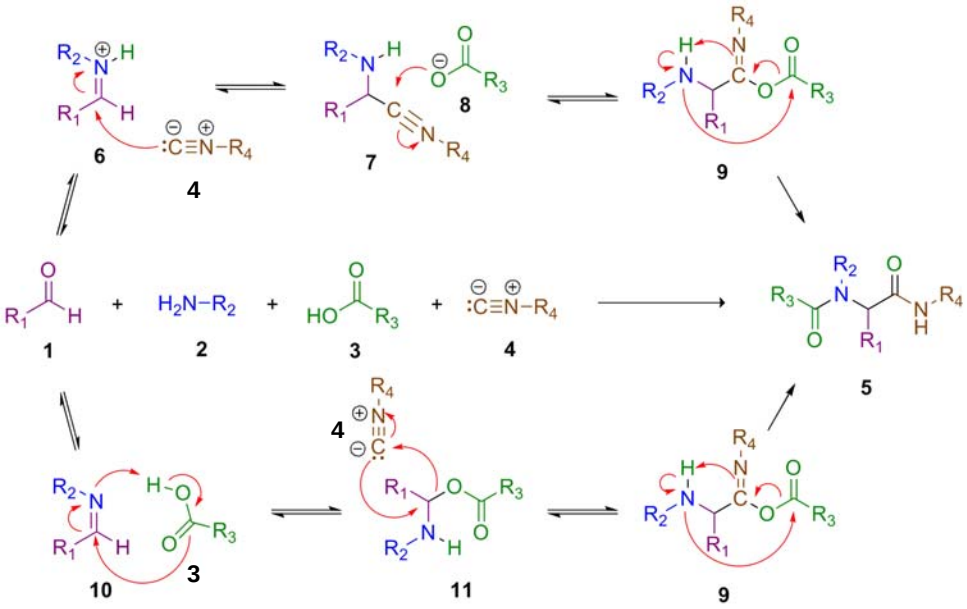
Major advances in the scope of the Ugi reaction have occurred only within the last 20 years, mainly because of the limited availability of isocyanides and poor stereocontrol. In the mid 1900's, only a few isocyanides were available. Today, about 380 isocyanides are commercially available.[5] Development of stereocontrol has been difficult due to incomplete knowledge of the reaction mechanism. Despite the similarities between the Passerini and Ugi reactions, methods of stereocontrol have not been interchangeable.[6] Techniques used in attempts to control enantioselectivity in the Ugi reaction have included Lewis acid catalysts and chiral auxiliaries.[6] Since a variety of functionality can be incorporated into the products, concurrent reactions are possible. Pre- and post-condensation modifications, including other multicomponent reactions (MCRs), can be performed to yield a variety of heterocyclic compounds. These compounds can then serve as scaffolds for the synthesis of natural products, therapeutic agents, and combinatorial libraries.

STEREOCONTROL

Two possible mechanisms for the Ugi reaction have been postulated.[7] In both mechanisms, the first step involves condensation of aldehyde **1** and amine **2**, followed by protonation of the imine by **3** (**Scheme 2**). The debate is whether the next step involves introduction of the carboxylic acid to **10**,

causing isocyanide **4** to react with **11** via an S_N2 mechanism, or whether isocyanide **4** first undergoes nucleophilic addition to imine **6**, followed by the addition of carboxylate **8** to **7** (**Scheme 2**). Experiments supporting the formation of intermediate **7** versus **11** have not been performed.[8] The lack of mechanistic studies could be attributed to the occurrence of competing mechanisms.[7] Combinations of three of the four components involved in the Ugi reaction are known to be involved in other MCRs (i.e. Passerini).[9]

Scheme 2. Postulated mechanisms of the U-4CR



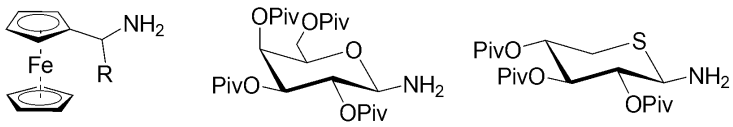
Lewis Acid Catalysts and Chiral Auxiliaries

Although stereocontrol of the Passerini reaction with chiral Lewis acid catalysts has been demonstrated, these catalysts usually show little to no effect on the Ugi reaction.[10] Titanium chloride can greatly improve condensation yields with aromatic aldehydes, but only modest enantioselectivity was observed (<11:1).[11] The first attempts to influence the stereoselectivity of the Ugi reaction utilized combinations of one or more chiral starting materials. Only moderate enantioselectivity (<10:1) was achieved in most cases. Lower temperatures (< –30 ºC) in conjunction with low concentrations of the isocyanide component often enhanced selectivity. This enhancement was most likely because of preferential formation of the kinetic product. Different chiral auxiliaries based on the components of the Ugi reaction were developed. Of these auxiliaries, chiral amine auxiliaries and bifunctional agents offered the best stereocontrol, with the added advantage that cleavage of these auxiliaries allowed for further modifications.

Some examples of chiral amine auxiliaries are shown in **Chart 1**. The first examples were α-alkylferrocenylamine derivatives **12**, which afforded excellent enantioselectivity (>99:1),[12] but moderate yields (46-59%) because of harsh cleavage conditions.[13] Recent experiments have used aminoglycosides as chiral auxiliaries. Use of pivaloyl galactopyranosylamine **13** with zinc chloride etherate in

stoichiometric amounts could produce *R*-configured products with very good enantioselectivity (>91:9, 43-83% yield);[14] with an arabinosyl derivative, the *S*-configured products could be obtained with excellent selectivity (>96:4, 85-91% yield).[15] One drawback, however, was that two separate steps were required to cleave the auxiliary. Currently, a thiolated xylopyranose derivative **14** has been developed to improve cleavage. An added advantage is that both D- and L-xylose auxiliaries can be prepared, so either *R*- or *S*-configured products can be obtained with good stereoselectivity (96:4, 91.8% yield).[16]

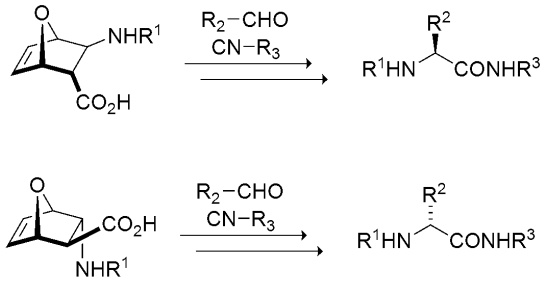
Chart 1. Examples of amine auxiliaries



12 **13** **14**

Bifunctional reagents are also being explored for stereocontrol in the Ugi four-center-three component reaction (U-4C-3CR). Some success was found with the preformed imines, but only the glycosyl auxiliary systems showed more than modest stereocontrol (>90:10).[17] With α-amino acids moderate selectivity (>80:20) could be obtained in conjunction with sterically hindered aldehydes and isocyanides, but this limited the scope of the starting materials.[18] The most recently developed bifunctional reagents were bicyclic β-amino acids (**Scheme 3**).[19] These were utilized in Ugi five-center-four-component reactions (U-5C-4CR), in which the solvent played a role as a proton donor.[20] The relatively rigid systems allowed for better control of the attack of the other components. Removal of the auxiliary could be accomplished under relatively mild conditions. By varying whether the amine was in the *exo* or *endo* position, either *R* or *S* configurations could be obtained in good yields and excellent enantioselectivity (> 95:5).[19]

Scheme 3. Ugi 5C-4CR with bicyclic β-amino acids



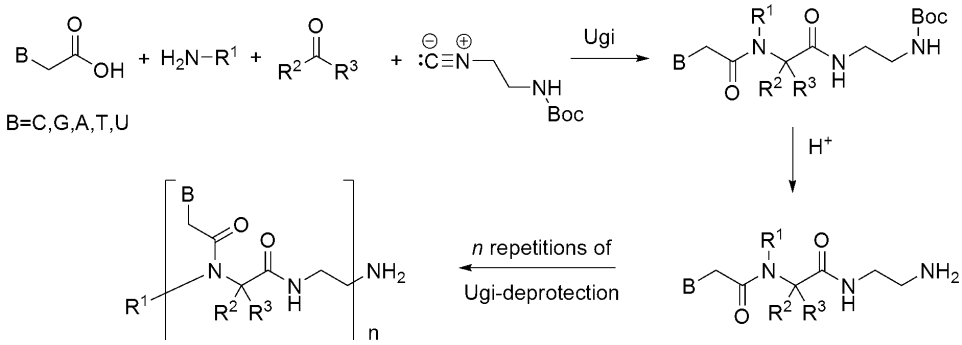
MODIFICATIONS AND APPLICATIONS

Tandem Multicomponent Reactions

One of the attractions of the Ugi reaction is the possibility of tandem MCRs. The inherent problem with this technique is that as the number of components increase, so do the number of competing side reactions. If a protected amine is included on one of the reagents, sequential Ugi condensations can be performed. This is referred to as the homo-Ugi or Ugi eight-component reaction

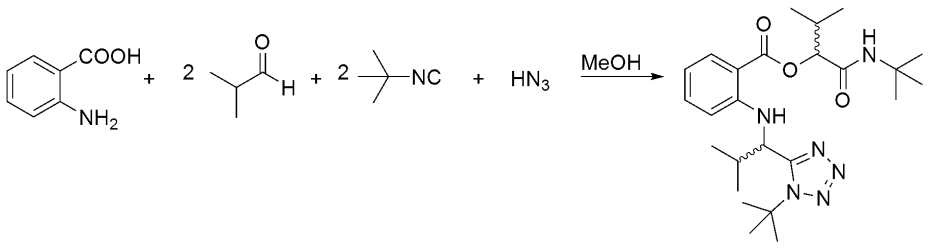
(U-8CR, **Scheme 4**).[21] After each condensation, the deprotected amine can be used as a component in a subsequent Ugi reaction. The incorporation of purine or pyrimidine derivatives on the carboxylic acid component can be used to generate peptide-nucleic acid oligomers.[22]

Scheme 4. The Ugi-Ugi Reaction (U-8CR)



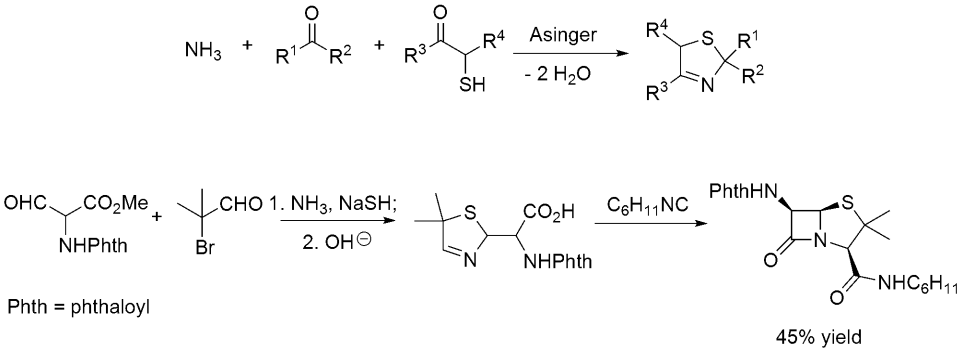
The union of the Ugi and the Passerini reactions yields the Ugi Seven-Center-Six-Component reaction (U-7C-6CR, **Scheme 5**).[24] This reaction is particularly advantageous because it is highly selective for the desired product, resulting in good yields and little to no byproduct.[23] One application for this technique is the synthesis of sterically strained α,α-dialkyl amino acid derivatives, which can be used to control conformations of peptides.[23] If the carboxylic acid component is replaced with hydrazoic acid, tetrazolyl derivatives can be synthesized.[24]

Scheme 5. The Tandem Ugi/Passerini Reaction (U-7C-6CR)



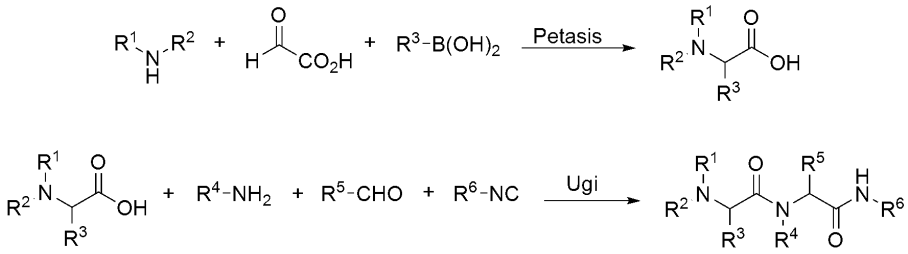
The combination of the Asinger and the Ugi reaction forms the Ugi Eight-Center-Seven-Component Reaction (U-8C-7CR, **Scheme 6**).[25] The Asinger product functions as an imine in the Ugi reaction and also adds the advantage of incorporating thioheterocycles into the final product. This technique can be utilized in synthesizing libraries of penicillin derivatives.[26]

Scheme 6. The Asinger reaction and the U-8C-7CR



An Ugi condensation can be preceded by a Petasis boronic-Mannich reaction to yield an Ugi Seven-Center-Six-Component Reaction (U-7C-6CR, **Scheme 7**).[27] The advantage of this technique is that the Petasis reaction can be stereoselective, establishing the stereocenter of the carboxylic acid.[28] This allows for more stereocontrol of the dipeptide products. By using a hydrazine derivative in the Petasis reaction, the synthesis of antimicrobial aza-β-lactams can be achieved.[29]

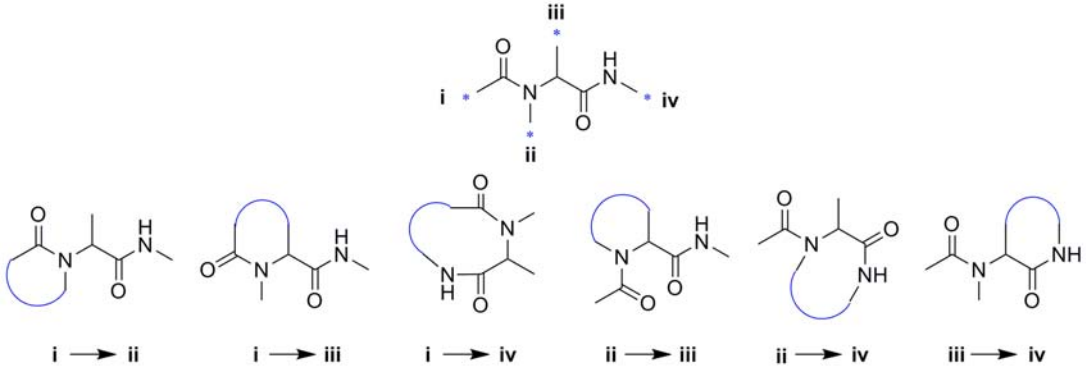
Scheme 7. The Petasis Reaction and the U-7C-6CR



Cyclization

Most modifications of Ugi products involve cyclizations to form diverse heterocyclic scaffolds. When these techniques are used in conjunction with bifunctional reagents and substituted aryl groups, a multitude of polycyclic heterocycles can be obtained. The skeletal structure of the Ugi product lends itself to four possible cyclization points (i-iv) and six different cyclic derivatives (**Scheme 8**).[30]

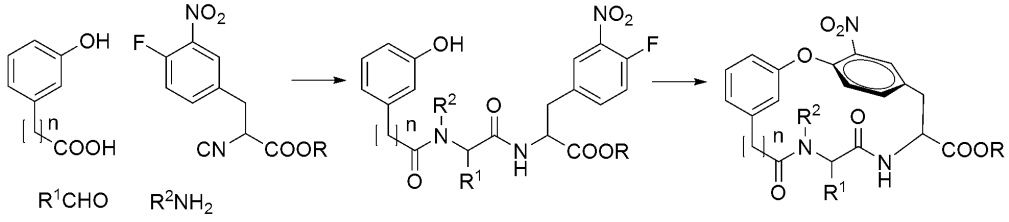
Scheme 8. Possible cyclic scaffolds available via post-modification of U-4CR



One of the most common post-condensation modifications in the Ugi reaction is referred to as the Ugi/Deprotect/Cyclization method (UDC).[31] A protected amine is included as a functional group on one of the starting reagents. When it is deprotected, other functional groups within the molecule allow for a subsequent cyclization. Removal of an auxiliary generates an opportune position for cyclization. Other methods utilize nucleophilic aromatic substitution to perform amination of aryl rings.[32]

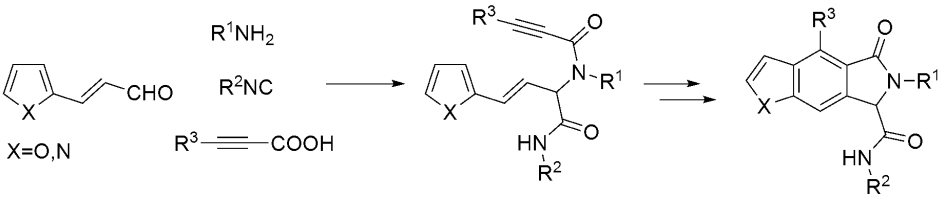
Another method of cyclization is the intramolecular nucleophilic aromatic substitution reaction (S_NAr, **Scheme 9**).[33] Formation of biaryl ether bridges allow for the synthesis of macrocycles found in antibacterials. This macrocycle has structure very similar to the biaryl ether macrocycles found within compounds such as vancomycin. Based upon the similarity in structure, this synthetic technique could be used to generate libraries of vancomycin derivatives.

Scheme 9. Macrocyclization by S_NAr reaction

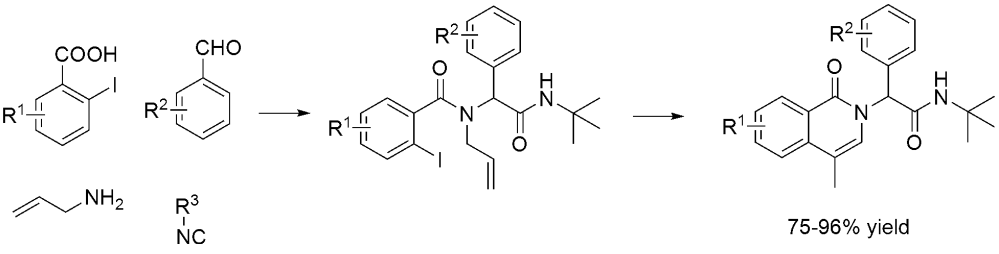


Various cycloadditions can be performed, such as the intramolecular Diels-Alder reaction (**Scheme 10**).[34] Benzofuran and indole derivatives can be formed by incorporating either a furan or pyrrole in the aldehyde. These heterocycles can be found within a variety of therapeutics. Other techniques involve metal-catalyzed cycloadditions. The Ugi/Heck tandem reaction (**Scheme 11**) can be used to produce isoquinoline derivatives.[35] These scaffolds are present in a number of natural products and therapeutic reagents.[35]

Scheme 10. Diels-Alder cyclization of Ugi product



Scheme 11. Tandem Ugi/Heck coupling reaction

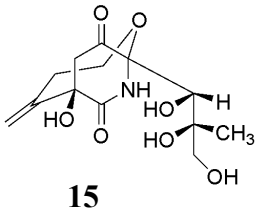


Natural Products and Libraries

The Ugi reaction has been applied in the synthesis of many natural products, such as bicyclomycin **15**, furanomycin **16**, penicillin **17**, and ecteinascidin 743 **18** (**Chart 1**).[36] Because of the

ability to incorporate a variety of functionality and modifications, the heterocyclic scaffolds for these natural products can be derivatized, generating libraries of analogues for screening.

Chart 2. Natural products synthesized via Ugi reaction



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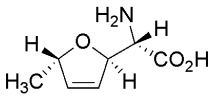

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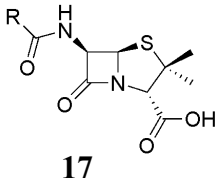

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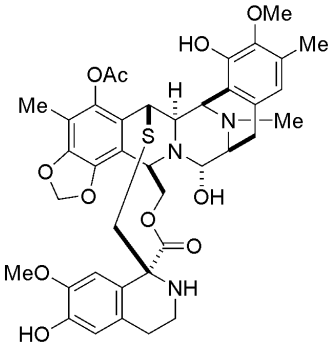

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CONCLUSION

Developments in the Ugi reaction have greatly increased within the last decade. Although more development is needed, the potential for the synthesis of a variety of heterocyclic compounds fuels interest in further research. The ability to perform tandem reactions to construct complex heterocyclic scaffolds makes the Ugi reaction a potentially powerful synthetic tool.

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