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Applications of the Ugi reaction with ketones

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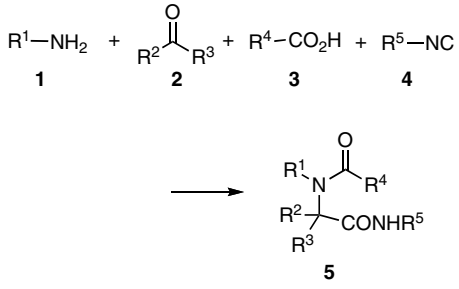
ABSTRACT

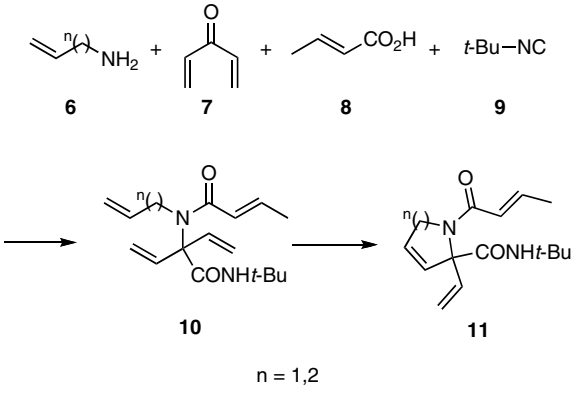
A convenient synthesis of highly functionalized, α,α-disubstituted amino acid amide derivatives has been accomplished by using cyclic and acyclic ketones as the carbonyl inputs in the Ugi multicomponent reaction. An application of this extension of the Ugi reaction to the synthesis of α,α-divinyl amino acids that may be cyclized via ring-closing metathesis to provide highly substituted pyrrolidines is described.

The design and development of convergent strategies to synthesize diverse arrays of drug-like compounds for biological screening is an important objective in contemporary chemical biology and medicinal chemistry. In this context, the use of multicomponent reactions (MCRs),[1] followed by post-condensation modifications via various ring-forming reactions, has proven to be a powerful tool as such processes can rapidly lead to the generation of libraries of functionalized compounds with diverse heterocyclic scaffolds. Indeed, our group has long had an interest in discovering new MCRs as well as expanding the scope of existing ones to rapidly access both alkaloid and drug-like motifs.[2,3]

The Ugi reaction is arguably one of the most important MCRs, and it is widely used in the pharmaceutical industry for preparing collections of compounds.[4] This powerful reaction involves a one-pot condensation of an amine **1**, a carbonyl compound **2**, a carboxylic acid **3**, and an isocyanide **4** to provide a substituted peptide-like product **5** (Scheme 1). Although the Ugi MCR has proven to be quite versatile, there are some limitations that become apparent upon examination of the literature. For example, the reaction is widely applicable to a variety of readily available amines, carboxylic acids, and aldehydes, but commercial access to isocyanides is more restricted than for the other three components. Moreover, it is often desirable to convert the initially formed amide into carboxyl derivatives and other functional groups. The latter issue has been nicely addressed by the invention of a number of so-called convertible isocyanides that can be elaborated after the condensation into various functional groups.[5] Aldehydes are widely used as components, but there are relatively few examples of the use of ketones as inputs. For example, Ugi reactions with simple ketones



Scheme 1.



Scheme 2.

such as acetone, cyclopentanone, and cyclohexanone are known to proceed in high yields in one-pot reactions.[6] *N*-Methyl and

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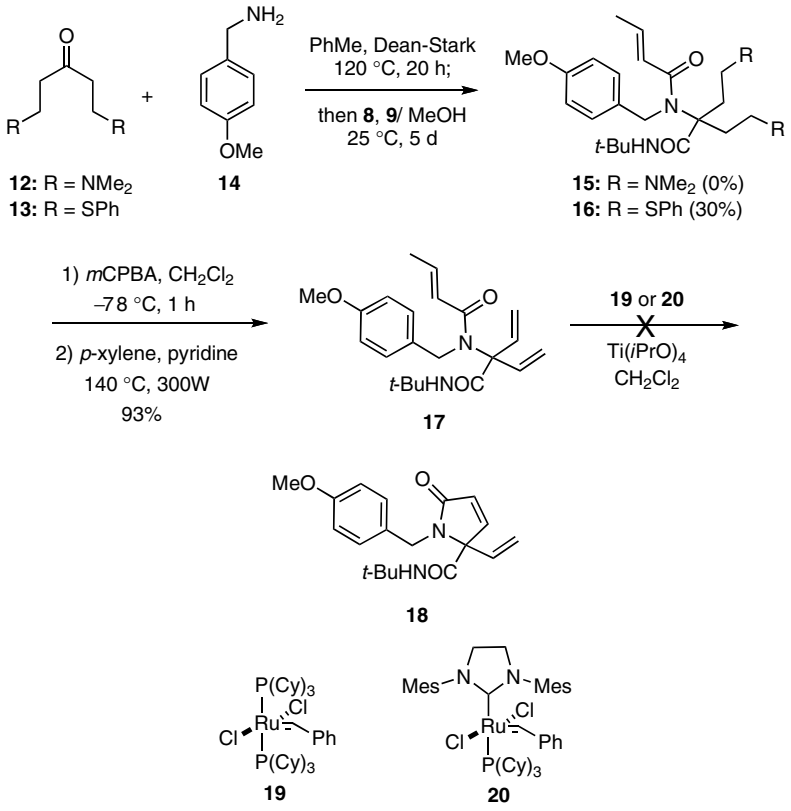
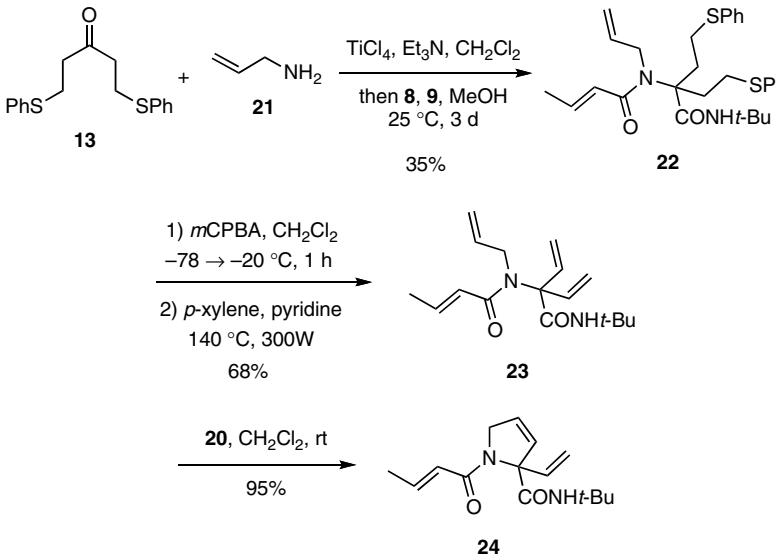
N-benzyl piperidones have also been employed as ketone components to give good yields of products,[7] and a library of spiro keto piperazines has been synthesized utilizing *N*-alkyl and *N*-aryl piperidones as the ketone components in an Ugi MCR.[8] However, use of acyclic dialkyl and diaryl ketones typically requires preformation of the imine intermediate in a separate step, and the yields of the Ugi adducts tend to be modest.[9]

During the course of recent efforts to develop facile approaches to alkaloid natural products and other nitrogen heterocycles, we were attracted to the possibility of employing an Ugi MCR followed by a ring-closing metathesis reaction (RCM).[10] In particular, we envisioned that an Ugi MCR using an unsaturated amine **6**, a functional equivalent of divinyl ketone **7**, which is known to be unstable,[11] crotonic acid (**8**) and an isocyanide like **9** would lead to an adduct **10** that might be cyclized via an asymmetric ring-closing metathesis (ARCM)[12] to generate highly substituted pyrrolidine and piperidine derivatives **11** in enantiomerically pure form (Scheme 2). This plan presented a unique opportunity to explore the scope of the Ugi MCR reaction with ketones and to probe the feasibility of cyclizing tetraene substrates containing prochiral vinyl groups in a ARCM. Although tandem Ugi/RCM processes to access bicyclic lactams (6- and 7-membered rings),[13] 9-membered



Scheme 3.



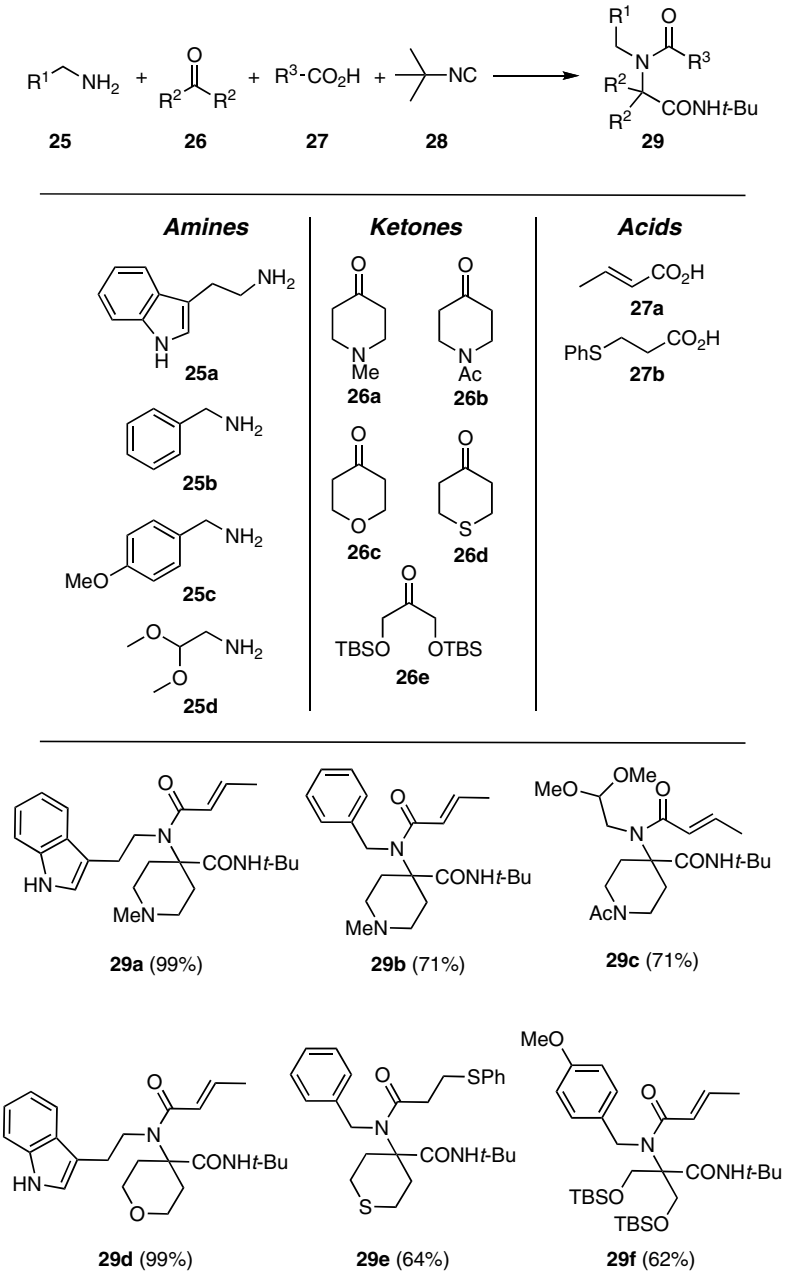
Scheme 4.

lactams,[14] and macrocyclic peptides[15] are known, the preparation of compounds related to **11** via Ugi/ARCM is not.[16] Herein, we wish to report some of our findings on the use of ketones in Ugi MCRs and on the synthesis of α,α-divinyl peptidic compounds that serve as substrates for RCM.

Our initial focus was upon acyclic ketones that could be easily refunctionalized via elimination reactions to provide the requisite α,α-divinyl amino acid derivatives. We quickly discovered, however, that acyclic ketones, such as **12**[17] and **13**[18] did not provide any of the desired Ugi products in one-pot reaction with the benzylamine **14** and the acid and isocyanide components **8** and **9**, respectively (Scheme 3). However, after some experimentation, we found that preforming the imine derived from **13** and **14** via Lewis acid catalysis ($TiCl_4$)[19] or azeotropic distillation followed by the addition of acid **8** and isocyanide **9** provided the adduct **16** in 30% yield. Because all attempts to preform the imine from **12** and **14** were unsuccessful, none of the Ugi adduct **15** could be prepared.

Compound **16** was readily transformed into the divinyl substrate **17** in excellent overall yield by S-oxidation with *m*CPBA to give an intermediate bis-sulfoxide that underwent facile elimination upon thermolysis. Although this elimination could be effected under conventional reflux conditions (18 h), it was considerably more facile in a microwave reactor (4 h). Unfortunately, in a series of exploratory experiments, we were unable to induce the RCM of **17** to give **18** using either Grubbs 1st or 2nd generation catalysts **19** and **20**, respectively; only unreacted starting material was recovered. Reasoning that the amide carbonyl oxygen atom of compound **17** might form an unreactive 6-membered chelated structure with the metal carbene on one of the vinyl groups,[20] Ti(*i*-PrO)$_4$ was added as a co-catalyst. However, this tactic was unavailing, and **17** was again recovered.

In order to obviate formation of unreactive chelates involving amides, a related sequence of reactions was conducted in which allylamine (**21**) was condensed with **13** in the presence of $TiCl_4$



Scheme 5.

and Et_3N, and the resultant imine was allowed to react with the carboxylic acid **8** and the isocyanide **9** to provide the allylic amine **22** in 35% yield (Scheme 4). Selective S-oxidation of the two sulfide moieties as before and subsequent thermolysis gave **23** in 65% yield. Gratifyingly, the RCM of **23** with Grubbs 2nd generation catalyst **20** (5 mol %) provided the highly substituted pyrrolidine **24** in 95% yield. A number of diverse and novel compounds related to **24** may be accessed by varying the acid and the isocyanide compounds in the Ugi reaction.

During the course of these studies, we discovered that a number of functionalized ketones containing heteroatoms could be employed that might serve as useful inputs in Ugi MCRs to give adducts in high yields according to the process generally depicted in Scheme 5. For example, the heterocyclic ketones 1-methyl-4-piperidone (**26a**), 1-acetyl-4-piperidone (**26b**), tetrahydro-4*H*-pyran-2-one (**26c**), and tetrahydro-4*H*-thiopyran-2-one (**26d**) were each found to participate in Ugi MCRs that proceeded readily in one-pot operations without preforming the ketimine.[21] Although the Ugi MCR involving **26a** has been recently reported to be efficient,[8] the only example of which we are aware of the use of **26d** is in a solid-phase Ugi process that was low yielding.[22] To our knowledge, there are no reports in the literature of employing **26b** and **26c** in Ugi MCRs; however, **26c** and **26d** have been used in some specialized isocyanide-based MCRs.[23,24] Protected dihydroxyacetone derivatives such as **26e** have not been used in Ugi MCRs. The amino inputs employed in these exploratory investigations were tryptamine (**25a**), benzylamine (**25b**), 4-methoxybenzylamine (**25c**), and aminoacetaldehyde dimethyl acetal (**25d**), whereas the carboxylic acid components were crotonic acid (**27a**) and β-phenylthiopropionic acid (**27b**). Because of its commercial availability, *tert*-butylisocyanide (**28**) was chosen as the universal isocyanide component. The utility of the method is exemplified by the preparation of the highly functionalized adducts **29a–f**.

In summary, we have found that a variety of ketones participate in either stepwise or one-pot Ugi MCRs to give good to excellent yields of adducts having a number of different functional groups that can be utilized in various post-condensation reactions. In one novel application of this strategy, we developed a route to highly substituted pyrrolidines via an Ugi reaction followed by a cyclization via RCM. The applications of these and related processes to the syntheses of biologically active natural and unnatural products are the subject of current investigations, the results of which will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (spectral and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.073.

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21. *General procedure for preparing* **29a–f**: The isocyanide **28** (1.1 mmol) was added to a solution of amines **25a–e** (1.1 mmol), ketones **26a–d** (1 mmol), acids **27a,b** (1.1 mmol) in MeOH (1 mL) at room temperature, and the solution was stirred for 18 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (20 mL). The organic solution was washed with satd aq $NaHCO_3$ (2×20 mL) and brine (20 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified either via flash column chromatography on silica gel (eluting with 1–2% MeOH in CH_2Cl_2) or by crystallization from EtOH.
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