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Sequential Ugi/Heck cyclization strategies for the facile construction of highly functionalized *N*-heterocyclic scaffolds ☆

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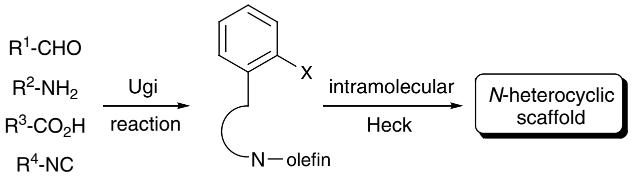
Abstract—A new strategy employing an Ugi four-component reaction and a microwave-assisted intramolecular Heck cyclization in a sequential fashion to access an array of *N*-containing heterocycles is reported. The two-step sequence generated compounds of significant molecular complexity from trivial starting materials in an expedient fashion with excellent yields. The route was also amenable to solid-phase chemistry demonstrating potential for library generation.

1. Introduction

The ability to incorporate high levels of molecular functionality in a single step continues to be an attractive feature of the Ugi multi-component condensation reaction.[1] In order to increase the 'biological attractiveness' of the Ugi adducts, many groups have recently reported examples of post-reaction manipulation focusing on substrate cyclization. These transformations include Diels–Alder reactions,[2] amino-cyclizations,[3] nucleophilic aromatic substitutions,[4] lactonizations,[5] and ring-closing metathesis.[6]

Our interest in the efficient generation of interesting cyclic nitrogen-containing motifs has led us to investigate a strategy, which relies on the sequential use of the Ugi multi-component reaction with the classical carbon–carbon bond-forming process, the Heck reaction. The palladium-catalyzed Heck reaction continues to prove itself as one of the most powerful methods to generate a carbon–carbon bond by exploiting the coupling of aromatic halides with olefins. The intramolecular version of this transformation has emerged as a potent synthetic tool in the generation of a variety of cyclic compounds.[7]



Scheme 1. General strategy.

The versatile strategy we now report allows the introduction of the olefin and aromatic halide functionalities within three of the four Ugi components. This allows us to control ring size and periphery features in the products based on the choice of the bifunctional starting materials. As demonstrated in Scheme 1, the Ugi reaction will generate a substrate containing both the olefin and the aromatic halide around a central nitrogen core. Subsequent cyclization via Heck reaction will produce the desired constrained *N*-scaffold. Although these two reactions have been utilized within the same synthetic sequence,[8] to the best of our knowledge this work represents the first examples of these two processes being carried out in a sequential fashion.

2. Results and Discussion

The initial systems we investigated were constructed utilizing α,β-unsaturated carboxylic acids (cyclic and

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Keywords: Ugi; Heck; multi-component reaction; solid-phase; scaffold.

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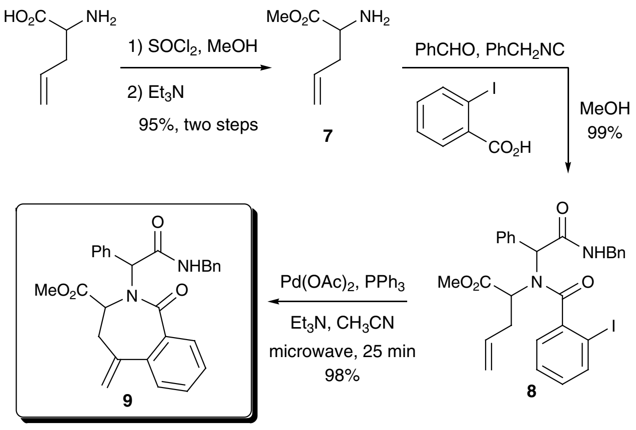
acyclic) as the olefin component, *o*-bromobenzaldehyde as the aromatic halide, benzyl amine, and benzyl isocyanide. The four-component Ugi condensation reactions afforded the desired products **1**–**3** in high yields (87–98%). These compounds were then subjected to microwave-assisted Heck reactions[9] and products were obtained in excellent yields (**4**–**6**) and high diastereoselectivities (**5** and **6**). Spirocyclic systems structurally similar to **5** and **6** have been generated previously, albeit with longer Heck reaction times ($\sim$18 h).[10] However, our microwave-mediated Heck reaction conditions circumvented lengthy reaction times ($\leqslant$2 h). It was one of the goals of our effort to produce scaffolds that are amenable to further manipulation. To this end, the cyclization of amides **1**–**3** generated two distinct olefin-containing spirocyclic systems and an α,β-unsaturated system, all primed for subsequent synthetic elaboration.

As stated previously, access to the other ring systems is done by simply manipulating the reactants for the multicomponent reaction. We ran the Ugi reaction of benzaldehyde, allylglycine methyl ester **7** as the amine component, benzyl isocyanide, and *o*-iodobenzoic acid to generate substrate **8** in high yield with a $\sim$1:1 diastereomeric ratio (Scheme 2). Intramolecular Heck reactions using amino acids as substrates have previously been reported.[11] As before, Heck cyclization on the Ugi product **8** proceeded smoothly to produce the seven-membered lactam **9** in excellent yield. The nature of the aromatic halide proved to be influential on Heck reactivity. Thus cyclization of aromatic iodide **8** was complete in only 25 min upon exposure to microwave irradiation under the same reaction conditions described above for systems **1**–**3**.

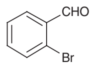
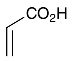
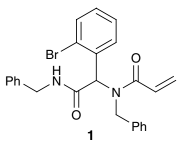
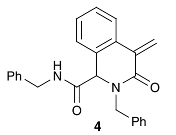
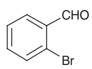
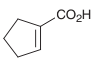
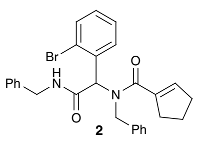
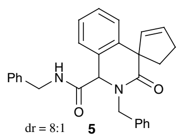
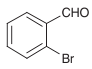
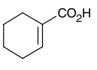
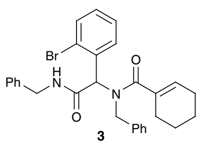
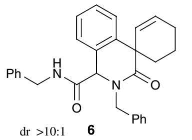


Scheme 2. Seven-membered ring closure.

An interesting variant of the multi-component Ugi chemistry is the five-centered-four-component reaction, which exploits an α-amino carboxylic acid as both the amine and the acid reactant.[12] For our system we used allyl glycine along with *o*-bromobenzaldehyde and benzyl isocyanide. This reaction, presumably, proceeds through a six-membered ring intermediate **10**, which then undergoes nucleophilic attack by methanol producing amino ester **11** in moderate yield. Substrate **11** cleanly underwent microwave-assisted Heck cyclization to generate **12** (under conditions described in Table 1) in 90% yield (Scheme 3).

Following the success of these examples in solution phase, we decided to test the effectiveness of our protocol on solid phase. Our solid-phase approach began with a two-step sequence, which coupled Wang resin

Table 1. Results of six-membered ring closure

Aldehyde	Amine	Isocyanide	Acid	Ugi product[a]	Ugi yield (%)	Heck product[b]	Heck yield (%)	Reaction time[c] (h)
	$PhCH_2NH_2$	$PhCH_2NC$		 1	87	 4	97	1
	$PhCH_2NH_2$	$PhCH_2NC$		 2	96	 dr = 8:1 5	98	2
	$PhCH_2NH_2$	$PhCH_2NC$		 3	98	 dr >10:1 6	91	2

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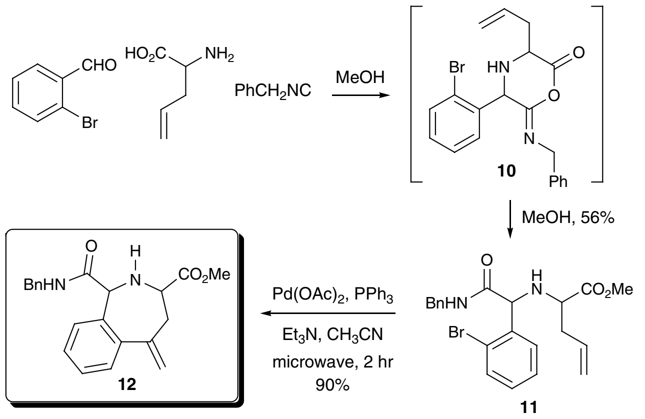
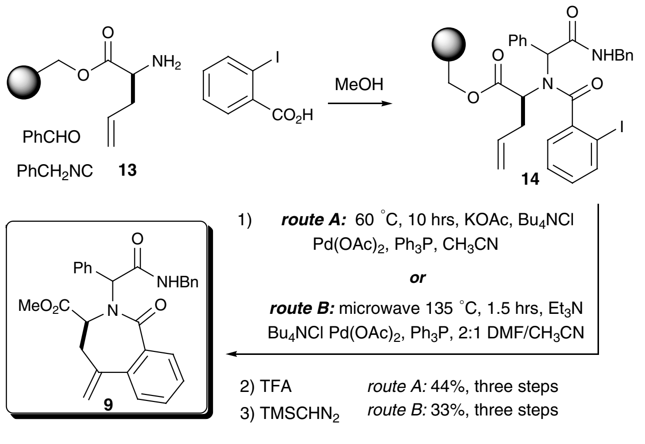
[a] Ugi multi-component reactions were carried out in MeOH at rt with reaction times ranging from 36 to 50 h; all products were isolated via flash chromatography.

[b] Diastereomeric ratios were obtained following the filtration through a small plug of silica.

[c] Microwave-assisted Heck reactions were carried out in CH_3CN at 125 °C for 1 h. The formation of the spirocyclic products **5** and **6** required two separate subjections to these conditions, therefore 2 h total reaction time. Similar reactions carried out in refluxing CH_3CN took 16–18 h for completion and afforded products with slightly lower yields (73–76%) and similar diastereoselectivities.



Scheme 3. Five-centered-four-component coupling route.



Scheme 4. Solid-phase route.

with Fmoc-protected (L)-allyl glycine mediated by 2,6-dichlorobenzoyl chloride.[13] Standard Fmoc deprotection yielded the desired resin-bound amino unit **13**. Ugi reaction was carried out using benzaldehyde, benzyl isocyanide, and *o*-iodobenzoic acid in a 1:1 mixture of $MeOH/CH_2Cl_2$.[3b–e,14] The resin-bound Ugi adduct **14** was washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×), and then subjected to two different solid-phase Heck cyclization conditions. The first set of reaction conditions utilized Bu_4NCl, KOAc, Ph_3P, and $Pd(OAc)_2$ in DMF[11,15] while the second example mimicked our solution phase conditions described above (systems **1**–**3**, **8**, **11**) with the sole difference being the addition of Bu_4NCl.[16] Following the Heck reactions, the resin was washed with DMF (3×), DMF/water 1:1 (3×), DMF (1×), MeOH (3×), and CH_2Cl_2 (3×). The cyclized adducts were cleaved from the resin (1:1 TFA/CH_2Cl_2) and the resulting acids were methylated utilizing (trimethylsilyl)diazomethane in MeOH, to produce ester **9** with moderate yields (33–44%) (Scheme 4).

3. Conclusions

We have demonstrated that the Ugi multi-component reaction followed by the intramolecular Heck cyclization is an efficient tool to obtain highly functionalized, constrained nitrogen containing scaffolds. This work represents another example of post-Ugi reaction manipulation, which further augments the recent examples of Ugi adduct cyclizations. Additionally, this methodology has been extended to solid-phase systems. More elaborate examples are being investigated along with exploring library generation. The results of this work will be reported in due course.

Acknowledgements

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flash chromatography (25% EtOAc/hexane) to give the pure product.

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16. It was found that the Heck cyclization did not go to completion (in 2 h) if Bu_4NCl was not added to the reaction mixture. It should be noted that both solid-phase Heck cyclizations utilized a twofold excess of both the Pd catalyst and PPh_3 with respect to their solution phase counterparts.