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A post-Ugi carbonylation/intramolecular amidation approach toward the synthesis of macrolactams

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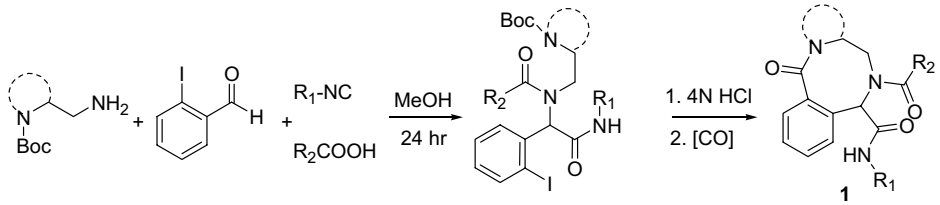
Abstract—An Ugi-deprotection–carbonylation/intramolecular amidation approach toward the synthesis of novel bicyclic and tricyclic macrolactams is described.

One of the most widely used multi-component reactions (MCRs) is the Ugi reaction,[1] and there have been several examples of its application towards the synthesis of libraries of compounds suitable for biological screening.[2] Despite its tremendous potential, the Ugi reaction is somewhat limited in that the products obtained are flexible and peptide like. One solution for making the products from an Ugi MCR more 'drug-like' is to constrain the initial product via a post-condensation modification. Thus, if one or two of the starting materials were to bear additional functional groups susceptible to reaction with each other after formation of the Ugi adduct, then cyclic structures should be produced, and several elegant examples of this approach have recently been reported.[3] In this report, we wish to describe an intramolecular carbonylation/amidation of a deprotected Ugi MCR product to provide macrolactams.

Seven to ten-membered lactams have gained importance as potential peptidomimetics,[4] as well as constituents of natural products,[5] and cell-signaling pathway inhibitors.[6] Approaches toward the synthesis of these rings have included attempted cyclizations of dipeptides[7] or intramolecular cyclization of an appropriately functionalized precursor moiety.[8] Recently, intramolecular Staudinger ligation,[9] ring-closing metathesis (RCM)[10] and intramolecular ring-expansion strategies[11] have been reported, which provide access to seven to nine-membered lactams.

Our approach toward the synthesis of macrolactams is shown in Schemes 1 and 2, and involves the use of either a bifunctional amine component or a bifunctional acid component in the Ugi MCR. Deprotection of the Ugi products resulting from the use of these inputs followed by a carbonylation/intramolecular amidation should afford macrolactams such as **1** and **2** with multiple points of diversity.

The Ugi MCR was found to be fairly general in scope as shown by the representative products (deprotected) in Table 1. Various carboxylic acids, isocyanides and



Scheme 1. Representative scheme for the Ugi-deprotection–carbonylation/intramolecular amidation using a bifunctional amine.

Keywords: Macrolactams; Intramolecular amidation; Ugi; Molybdenum; Microwave.
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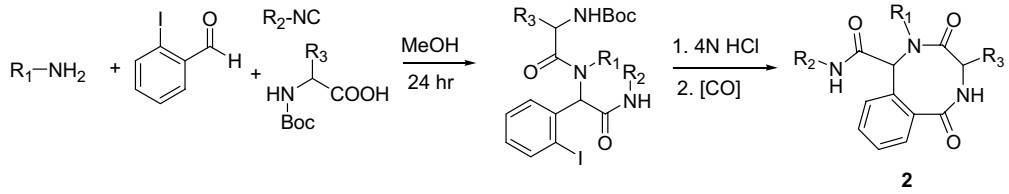

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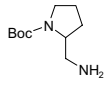
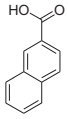
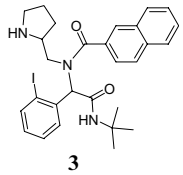
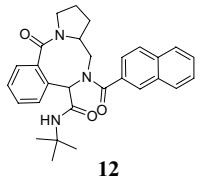
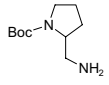
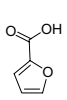
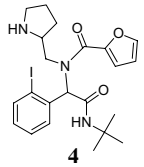
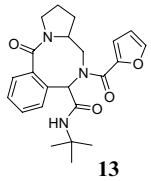
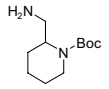
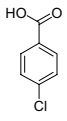
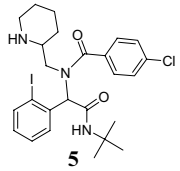
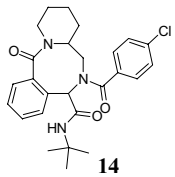
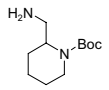
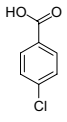
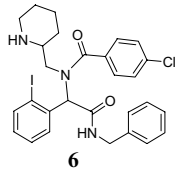
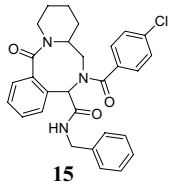
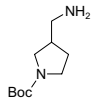
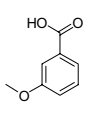
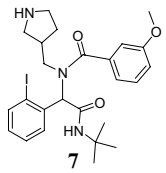
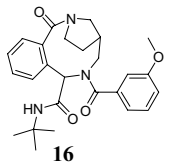
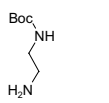
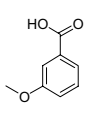
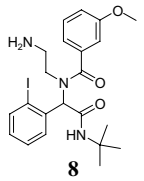
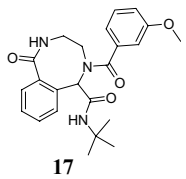
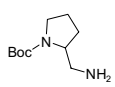
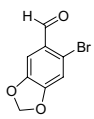
Scheme 2. Representative scheme for the Ugi-deprotection–carbonylation/intramolecular amidation using a bifunctional acid.

Table 1. Products obtained from the Ugi MCR (deprotected) and carbonylation/intramolecular amidation (CIA) sequence

Amine	Aldehyde	Isocyanide	Acid	Ugi product (deprotected)	Yield[a]	CIA product	Yield[a,b]
				 **3**	75	 **12**	65
				 **4**	69	 **13**	72
				 **5**	72	 **14**	77
				 **6**	66	 **15**	69
				 **7**	81	 **16**	33
				 **8**	70	 **17**	53
				**9**	85	**18**	62