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

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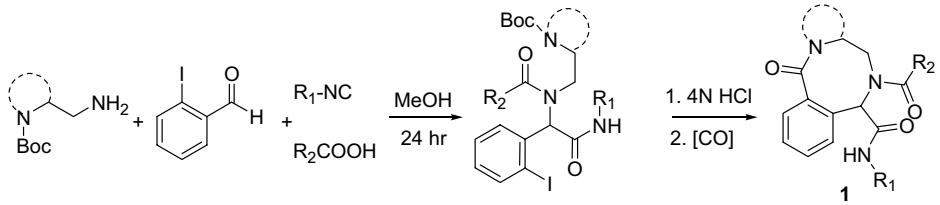
Abstract—An Ugi-deprotection–carbonylation/intramolecular amidation approach toward the synthesis of novel bicyclic and tricyclic macrolactams is described.

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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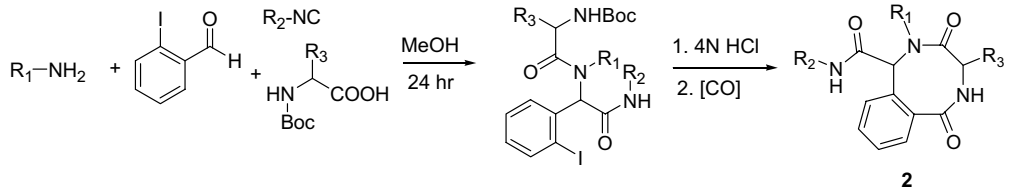

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Scheme 2. Representative scheme for the Ugi-deprotection–carbonylation/intramolecular amidation using a bifunctional acid.

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

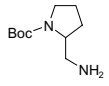
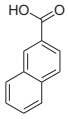
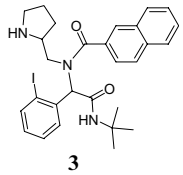
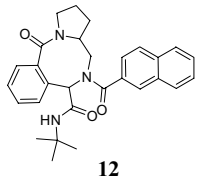
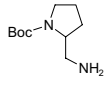
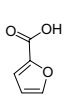
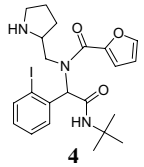
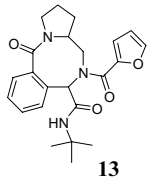
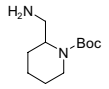
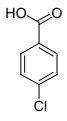
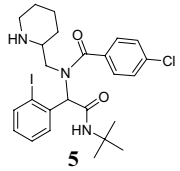
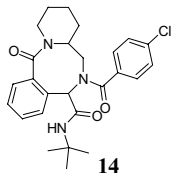
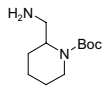
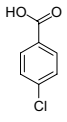
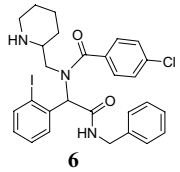
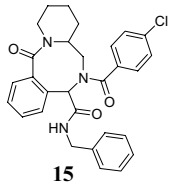
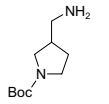
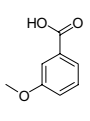
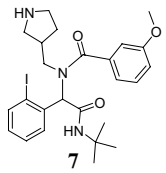
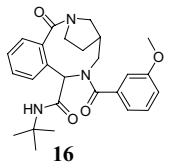
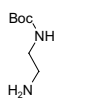
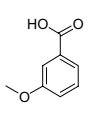
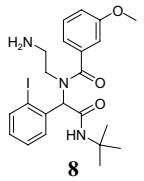
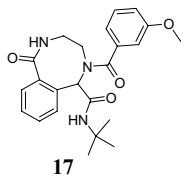
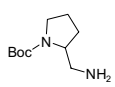
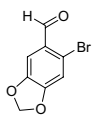
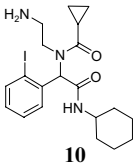
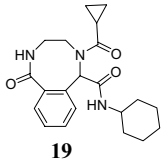
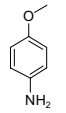
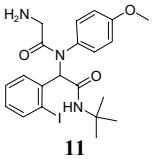
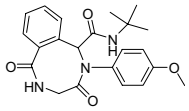
Amine	Aldehyde	Isocyanide	Acid	Ugi product (deprotected)	Yield[a]	CIA product	Yield[a,b]
				 **3**	75	 **12**	65
				 **4**	69	 **13**	72
				 **5**	72	 **14**	77
				 **6**	66	 **15**	69
				 **7**	81	 **16**	33
				 **8**	70	 **17**	53
				**9**	85	**18**	62

Table 1 (*continued*)

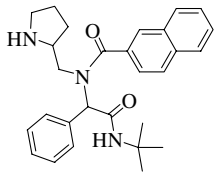
Amine	Aldehyde	Isocyanide	Acid	Ugi product (deprotected)	Yield[a]	CIA product	Yield[a,b]
				 **10**	88	 **19**	51
				 **11**	80	 **20**	70

[a] mixture of diastereomers, where applicable.
[b] Isolated yields.

amines were utilized and the products purified via sequential treatment with PS-trisamine[12] and MP-CO_3[13] to afford pure Ugi products in respectable yields as mixtures of diastereomers, where applicable.

Initial literature reports on the intermolecular amidation of aryl halides using Pd catalysis by Heck and co-workers,[14] were followed by the extension of this methodology to intramolecular amidation by Ban and co-workers.[15] Recently, Rh-catalyzed intramolecular carbonylation using aldehydes as a source of carbon monoxide has been reported[16]—however, this approach is restricted to the use of tosylated amines. Larhed and co-workers have reported the use of $Mo(CO)_6$ as a source of CO and demonstrated its application to intermolecular carbonylation and allylic alkylation.[17] Under these conditions, sterically hindered amines afforded poor results and the effect on sterically hindered halides was not reported.

Deprotection of the Ugi MCR products with 4 N HCl afforded the desired amine poised for the carbonylation/intramolecular amidation reaction. Several conditions were attempted to affect the carbonylation/intramolecular amidation of a model substrate **3**, and some general trends were apparent. The use of a $K_2CO_3/Pd(OAc)_2/Mo(CO)_6$ manifold as reported by Larhed and co-workers[17] in a single-mode microwave[18] resulted in predominant formation of the dehalogenated Ugi product **21**, along with trace amounts of **12**. A similar pattern was observed when the reaction was performed in a pre-heated oil-bath at 150 °C for 15 min.



21

Changing the base from K_2CO_3 to Cs_2CO_3 or DBU also resulted in formation of significant amounts of **21**, as did the use of no base. Further, the use of alternate Pd sources such as $PdCl_2$ (dppf) resulted in exclusive formation of **21**. Alterman and co-workers have recently reported the synthesis of phthalides and isoindolinones via the use of DIEA/DMAP/$Pd(OAc)_2$ and PPh_3 as an additive.[19] The use of these conditions for the transformation of interest in this study did not afford improved formation of **12** compared to **21**. To improve the absorption of the carbon monoxide generated via the decomposition of $Mo[CO]_6$, *n*-Bu_3N was used as an additive[14] and the reaction heated at 160 °C in diglyme for 15 and 60 min to afford significantly enhanced formation of **12**. The PPh_3 was found to be nonessential, and the optimal conditions for the carbonylation/intramolecular amidation were to heat the sterically hindered substrate with a mixture of $Mo[CO]_6/Pd(OAc)_2/n$-Bu_3N in diglyme at 160 °C for 1 h in a sealed tube.[20] Aryl bromides were also found to be effective substrates for the carbonylation/intramolecular amidation (e.g., **9**), though the reaction mixture had to be charged twice with $Mo[CO]_6$ and $Pd(OAc)_2$ to afford efficient conversion. The use of 3-aminomethyl pyrrolidine as the amine input afforded constrained nine-membered macrolactam, **16**. Further, the use of a *tert*-butoxycarbonyl-protected amino acid as the acid input, followed by deprotection and intramolecular amidation affords benzo[*f*][1,4]diazocine-1,4-dione, **20**. Depending on the chirality of the amine inputs used in this study, the Ugi-products as well as the macrolactams were obtained as mixtures of diastereomers.

The post-synthesis sample handling was fairly convenient and application of the reaction mixture on to a cation-exchange resin (Bond Elut™ SCX),[21] followed by elution with CH_3OH resulted in retention of the dehalogenated product as well as *n*-Bu_3N, allowing for facile purification of the macrolactam.

In conclusion, the synthesis of novel eight and nine-membered lactams with multiple sites of diversity has

been accomplished via a carbonylation/intramolecular amidation[22] of the product of an Ugi MCR.

Acknowledgements

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20. In all these experiments, similar results were observed using (pre-heated) oil-bath conditions and single-mode microwave irradiation. Performing the intramolecular amidation in a sealed tube for up to 24 h did not afford increased product formation compared to 1 h reaction time. To avoid the potential of plating out of Mo (Ref. 17) at elevated temperatures due to localized superheating in the microwave, oil-bath conditions were prefered for these transformations.
21. Bond Elut™ SCX columns were purchased from Varian Inc.
22. Typical procedure for the Ugi-deprotection–carbonylation/intramolecular amidation procedure: a solution of 1 equiv each of the amine, aldehyde, isocyanide and acid (1 mmol each) in 3 mL anhydrous CH_3OH was stirred at room temperature for 18 h. The solvent was evaporated, and the residue dissolved in 4 mL of 1:1 CH_2Cl_2–THF followed by the addition of PS-TsNHNH$_2$ (3 equiv) and MP-CO_3 (3 equiv). After stirring the reaction mixture for 4 h at room temperature, the reaction was filtered, and the resin rinsed with CH_2Cl_2 (2×2 mL) and THF (2×2 mL). The combined filtrate was concentrated to afford the pure Ugi product. Treatment of the Ugi product with 4 mL 4 N HCl/dioxane at room temperature for 6 h followed by evaporation of the solvent afforded the pure deprotected amine. The deprotected amine, $Pd(OAc)_2$ (5 mol %) and $Mo(CO)_6$ (0.5 equiv) were weighed into a high-pressure tube which was sealed and flushed with nitrogen. *n*-Bu_3N (3 equiv) and diglyme (1 mL) were added to the tube which was immersed in an oil bath, preheated to 160 °C. At the end of 1 h, the reaction was cooled, the reaction mixture filtered through a 0.5 μM syringe filter, and the solvent evaporated. The residue was dissolved in 1 mL CH_3OH and passed through a Bond Elut™ SCX column (5 g) and the first three rinses of 1 mL each were collected to afford the desired macrolactam. Purification of the combined washes, after evaporation, via flash chromatography afforded the desired macrolactam. Data for selected compounds: **8**: viscous light brown oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.02 (s, 1H), 7.95 (d, 1H), 7.87 (br s, 2H), 7.48 (t, 1H), 7.36 (t, 1H), 7.23(d, 1H), 7.02–7.15 (m, 4H), 5.17 (s, 1H), 3.81 (s, 3 H), 3.53–3.46 (m, 1H), 3.10–3.04 (m, 1H), 2.93–2.86 (m, 1H), 2.60–2.53 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 172.37, 169.85, 158.82, 140.21, 137.85, 137.52, 130.35, 129.16, 128.67, 119.21, 115.22, 113.27, 111.74, 102.25, 69.10, 55.34, 50.79, 41.69, 36.71, 27.95. Compound **10**: viscous colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6, T = 120 °C): δ 8.14 (br s, 1H), 7.97 (dd, 1H), 7.46 (dt, 1H), 7.33 (dd, 1H), 7.13 (dt, 1H), 5.92 (s, 1H), 3.63–3.70 (m, 2H), 3.11–3.02 (m, 1H), 2.98–2.90 (m, 2H), 2.61–2.53 (m, 2H), 1.80–1.53 (m, 5H), 1.36–1.12 (m, 6H), 0.92–0.74 (m, 4H). ^{13}C NMR (300 MHz, DMSO): δ 174.32, 173.51, 169.20, 169.14, 140.41, 140.11, 138.57, 137.55, 130.72, 130.46, 130.37, 129.21, 128.96, 103.09, 102.64, 67.27, 65.51, 48.28, 48.23, 42.57, 41.91, 37.54, 32.23, 32.18, 32.08, 25.30, 24.75, 24.63, 24.53. Compound **11**: viscous pale brown oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.25 (s,

2H), 7.98 (s, 1H), 7.84 (br d, 1H), 7.81 (d, 1H), 7.10 (t, 1H), 6.90–6.83 (m, 4H), 6.65 (br s, 1H), 6.07 (s, 3H),3.41 (d, 1H), 3.17 (d, 1H), 1.27 (s, 9H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 168.10, 166.06, 158.78, 139.15, 137.70, 131.74, 130.62, 130.30, 129.75, 129.63, 104.30, 68.16, 66.29, 55.14, 50.60, 28.39. Compound **17**: white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.52 (t, 1H), 8.39 (s, 1H), 7.66 (d, 1H), 7.62–7.56 (m, 2H), 7.48 (t, 1H), 7.36–7.31 (m, 3H), 7.08–7.04 (m, 1H), 5.31 (s, 1H), 3.98–3.92 (m, 1H), 3.75 (s, 3H), 3.63–3.55 (m, 1H), 3.51–3.39 (m, 2H), 1.28 (s, 9H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 168.36, 166.17, 166.03, 159.07, 142.18, 135.94, 131.73, 131.55, 129.31, 128.39, 122.71, 122.17, 119.30, 116.78, 112.44, 63.63, 55.17, 50.86, 40.81, 37.67, 28.28.