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SYNTHESIS OF SMALL AND MEDIUM SIZED 2,2-DISUBSTITUTED LACTAMS VIA THE "INTRAMOLECULAR" THREE COMPONENT UGI REACTION

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Abstract: A series of small and medium sized lactams were synthesized through the use of tethered keto-acids in an "intramolecular" multicomponent Ugi type reaction. This chemistry afforded five-, six-, seven- and eight-membered lactams in good yields. © 1997 Elsevier Science Ltd.

As part of our drug discovery efforts to produce unique peptide-like compounds as potential modulators of leukocyte trafficking,[1-6] it was envisioned that utilizing multicomponent reactions would afford compounds with amino acid-like backbones containing high levels of molecular diversity. To this end, a variety of 2,2-disubstituted lactams were synthesized with variations of both ring size and substitution at the amide nitrogens. Utilizing chemistry described by Ugi,[7,8] such molecules can be derived from a multicomponent condensation which constructs a complex molecule in a one step reaction. Muticomponent reactions have been quite fruitful for the convergent synthesis of a variety of heterocyclic ring systems including azetidinones,[9-11] pyrroles,[12] hydantoins,[13] piperazines[14] and benzodiazepines.[15] A recent report by Short and Majalli,[16] in which solid phase multicomponent reactions were used to assemble five and six membered lactams, has prompted us to reveal our findings in this area. Reported herein on the synthesis of some 2,2-disubstituted pyrrolidinones, piperidinones, azepinones, and azocanones via a three component Ugi condensation utilizing keto-acids. This is the first report of an intramolecular Ugi reaction leading to medium sized (seven and eight membered) lactams.

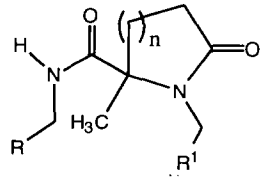
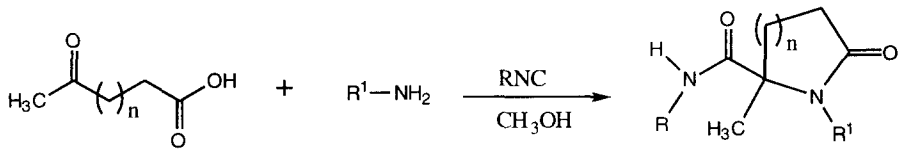


Figure: n = 1, 2, 3, 4

Standard Ugi reaction conditions employ four components, an acid, an amine, an aldehyde or ketone, and an isocyanide.[7] In the chemistry reported herein, the acid and ketone are tethered with the appropriate spacing to

afford five, six, seven and eight membered lactams. Reactions of amines with keto-acids such as levulinic acid (4-oxopentanoic acid), 4-acetylbutyric acid, 6-oxoheptanoic acid, and 7-oxooctanoic acid in methanol lead to the facile formation of the desired imine. Addition of an isocyanide to the reaction lead to the formation of the target molecules (entries **1 - 14, Scheme 1, Table**). Formations of the five and six membered systems proceeded quite well, while as predicted, the more difficult synthesis of the medium sized rings proceded in slightly lower yields. In fact, earlier reports of this chemistry via solid phase synthesis reported that the formation of seven membered rings proved unsuccessful.[16] This chemistry affords a facile route to the synthesis of a series of medium sized lactams (seven and eight membered rings) which are otherwise difficult systems to synthesize via alternative routes.[17] It is crucial to note that high dilution was necessary, especially in the formation of the seven- and eight-membered lactams to promote intramolecular cyclization.

Scheme 1



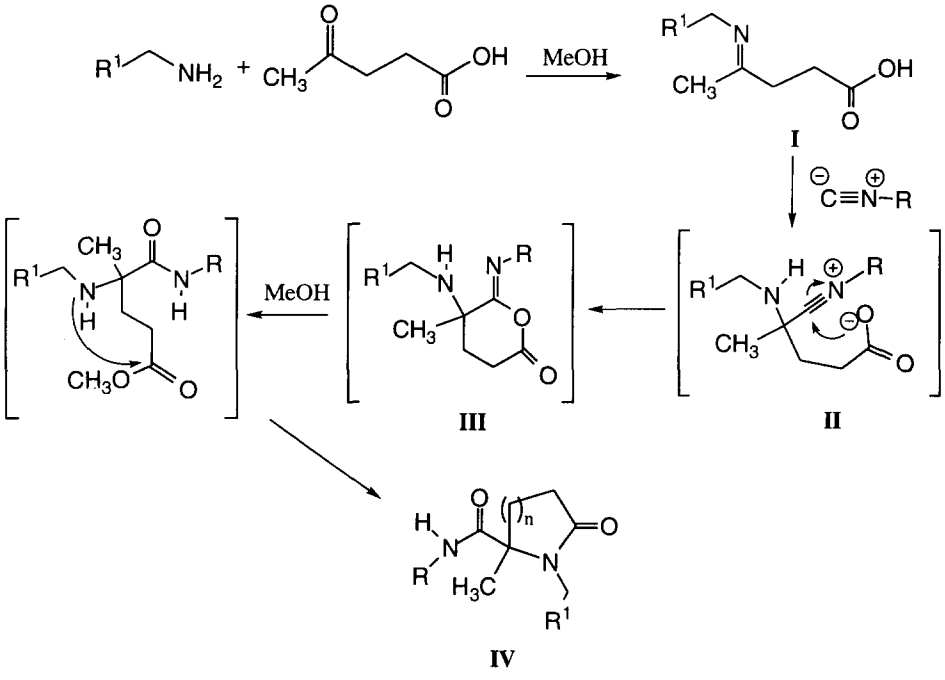
n = 1, 2, 3, 4

Table: Yields of the formation of lactams via the three component intramolecular Ugi reaction.[18]

entry	n	R^1	R	yield
1	1	benzyl	benzyl	62%
2	1	benzyl	n-butyl	64%
3	1	benzyl	4-(2-ethyl)morpholine	61%
4	1	4-(3-propyl)morpholine	benzyl	79%
5	1	4-(3-propyl)morpholine	n-butyl	76%
6	2	benzyl	benzyl	62%
7	2	benzyl	n-butyl	58%
8	2	benzyl	4-(2-ethyl)morpholine	61%
9	2	isobutyl	benzyl	54%
10	2	4-(3-propyl)morpholine	benzyl	60%
11	3	benzyl	benzyl	23%
12	3	benzyl	n-butyl	70%
13	4	4-(3-propyl)morpholine	n-butyl	41%
14	4	isobutyl	benzyl	53%

Methanol proved to be a crucial reaction component as it is postulated to play a catalytic role in the reaction mechanism (**Scheme 2**). The reaction proceeds first through the formation of imine **I**. Subsequent additon of the isocyanide results in the formation of nitrilium intermediate **II**. Intramolecular attack of the carboxylate on the nitrilium carbon results in cyclic intermediate **III**. Addition of methanol to the acyl center results in ring opening which is then quickly followed by lactam formation (product **IV**). Attempts at utilizing a less nucleophilic polar protic solvent, *t*-butanol, led to no product formation.

Scheme 2



Representative reaction procedure:

To a stirred solution of keto-acid (5 mmol) in methanol (25 mL) at room temperature was added amine (6.25 mmol) at once and stirred for 45 minutes to ensure imine formation. The isocyanide (5 mmol, CAUTION: STENCH) was added at once and the reaction was stirred at room temperature for 48 hrs. Excess methanol was removed under reduced pressure and the reaction residue was brought up into 50 mL of CH_2Cl_2.

For entries **1**, **2**, **3**, **6**, **7**, **9**, **11**, **12** and **14**, which do not contain basic residues, the mixture was washed once with 10% (aq) HCl (50 mL) which ensures removal of the starting amine. The organic layer was separated and washed twice with 6 M NaOH (aq) (50 mL) which ensures the removal of the starting keto-acid. The organic layer was dried over Na_2SO_4, and the solvent was removed. Pure lactam was obtained via recrystallization (in most cases from 20% hexanes/CH_2Cl_2).

For entries containing basic residues (**4**, **5**, **8**, **10**, **13**) the organic layer was extracted with 50 mL 10% HCl (aq). The acidic aqueous layer was separated and subsequently neutralized by the slow careful addition of solid KOH to an ultimate pH of 13. The product was then extracted from the water layer with ethyl acetate (100 mL). The organic layer containing the product was dried over Na_2SO_4. The solvent was removed under reduced pressure and the resuting product was recrystallized.

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(18) All compounds shown have produced analytical data including ^{1}H and ^{13}C NMR, MS, and C,H, N combustion analysis consistant with their structures.

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