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A Facile Synthesis of *N*-Carbamoylmethyl- α -aminobutyrolactones by the Ugi Multicomponent Condensation Reaction §

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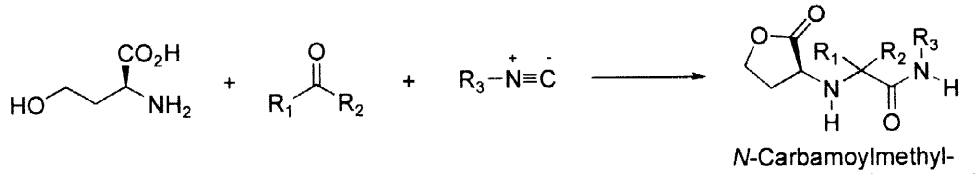
Abstract

A new method of various *N*-carbamoylmethyl-α-amino-butyrolactones **4** utilizing the intramolecular Ugi five-center-three-component condensation reaction starting from L-homoserine was developed.

Keywords: Amino acids and derivatives ; Condensations ; Lactones ; Ugi-Passerini reactions

Recently, the combinatorial synthesis of chemical libraries of small organic molecules has received much attention as a new tool for drug discovery.[1-4] One of important strategy for the generation of chemical libraries involves the use of multi-component condensation reaction, the simultaneous reaction of several reactants in a one pot procedure.[5,6] Among many multi-component reactions, the four-component condensation reaction first discovered by Ugi has been especially exploited by numerous organic chemists due to it's versatility and preparative advantages.[7-10] The typical Ugi reaction is the condensation reaction of an amine, an aldehyde or ketone, an isocyanide, and a carboxylic acid to form an α-aminoamide.



1 2 3 *N*-Carbamoylmethyl-α-aminobutyrolactones **4**

Scheme 1

§ *Dedicated to Professor H. Simon.*

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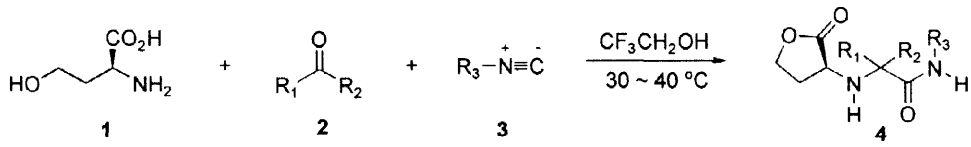
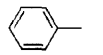
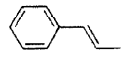
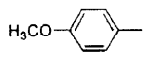
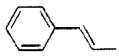
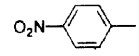
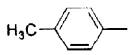
Thus this four-component condensation affords easy and effective synthesis of a variety of heterocyclic ring system including lactams,[11-14] hydantoins,[15,16] tetrazoles,[17] imidazoles,[18] pyrroles,[19-21] benzodiazepines,[22] and diketopiperazines[23] from simple building blocks. We wish to report herein an efficient route to *N*-carbamoylmethyl-α-aminobutyrolactones **4**, a new member of this series, in which the key step was an intramolecular Ugi reaction starting from L-homoserine **1**, aldehydes or ketones **2**, and isocyanides **3** (**Scheme 1**). The compound **4** of general structure are of interest due to certain biological activity such as immuno suppressant, antiallergy, asthma, and antineoplastic agents.[24,25] The reaction in 2,2,2,-trifluoroethanol expectedly provided the desired *N*-carbamoylmethyl-α-aminobutyrolactones **4** in moderate to excellent yield as a mixture of diastereomers in varying ratios as shown in the **Table.**

Table



1 **2** **3** **4**

Entry	R_1	R_2	R_3	Reaction time (hr)	Yield (%)	Ratio[a]	Entry	R_1	R_2	R_3	Reaction time (hr)	Yield (%)	Ratio[a]
4a	$CH_3(CH_2)_2$-	H	$(CH_3)_3C$-	18	93	4:1	4l	$(CH_3)_3C$-	H		48	78	99:1[b]
4b	$(CH_3)_2CH$-	H	$(CH_3)_3C$-	70	71	97:3[b]	4m		H		12	68	2 : 1
4c	$(CH_3)_3C$-	H	$(CH_3)_3C$-	70	73	99:1[b]	4n		H		19	77	6 : 1[b]
4d		H	$(CH_3)_3C$-	12	62	2:1	4o		H		24	69	8 : 1
4e		H	$(CH_3)_3C$-	19	69	2:1[b]	4p				48	87	--
4f		H	$(CH_3)_3C$-	14	59	2:1	4q		H	EtO_2CCH_2-	12	78	3 : 1
4g		H	$(CH_3)_3C$-	14	62	2:1	4r	$CH_3(CH_2)_2$-	H	$TosCH_2$-	60	73	3 : 1
4h		H	$(CH_3)_3C$-	12	52	2:1	4s	$(CH_3)_2CH$-	H	$TosCH_2$-	94	97	7 : 1
4i			$(CH_3)_3C$-	48	42	-	4t	$(CH_3)_3C$-	H	$TosCH_2$-	94	92	3 : 1
4j	$CH_3(CH_2)_2$-	H		12	68	2:1	4u		H	$TosCH_2$-	47	71	8 : 1
4k	$(CH_3)_2CH$-	H		58	48	1:1	4 v			$TosCH_2$-	70	72	--

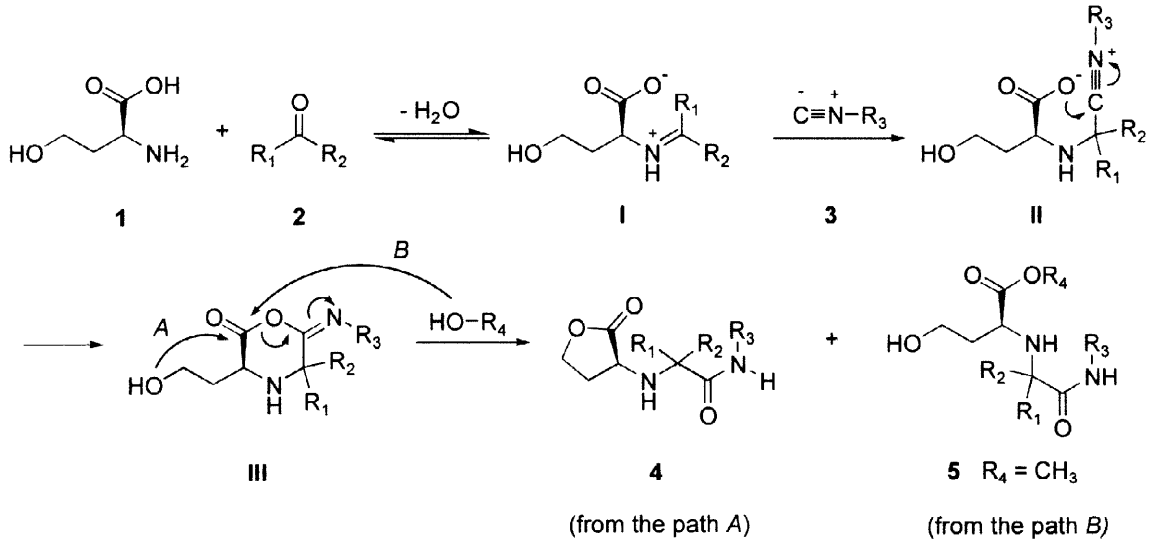
[a] The diastereomeric ratio was determined by ^1H NMR of the crude mixture.

[b] The diastereomeric ratio was determined by GC of the crude mixture.

[c] All new compounds were characterized by IR, ^1H and ^{13}C NMR, and HRMS data.

The overall route is summarized in **Scheme 2**. The addition of the isocyanide **3** to the prepared imine **I** gave the intermediate **II**. The attack of the carboxylate on the nitrilium carbon of **II**,

followed by the hydroxy addition on the carboxylate carbon of **III** resulted in formation of **4** by the double intramolecular attacks through the path *A*. Using 2,2,2,-trifluloroethanol as a solvent for this reaction is critical to have the desired sole product and better yields.



Scheme 2

When methanol was used as a solvent, the ring opening compound **5** in fair amounts as well as **4** was formed by the methanol attack to the carboxylate carbon of the intermediate **III** by the path *B*. The reaction yields largely depend on the chosen aldehydes and isocyanides respectively. A very interesting aspect observed in these reactions is that the reaction with the hindered aldehydes (entry **4b**, **4c**, and **4l**) proceeded with high diastereoselectivity, probably due to steric factors. The relative stereochemistry of the diastereoisomers obtained has been confirmed by X-ray analysis of the major stereoisomer of **4b**, which has *R*-configuration at the carbon 5 position (**Figure**).

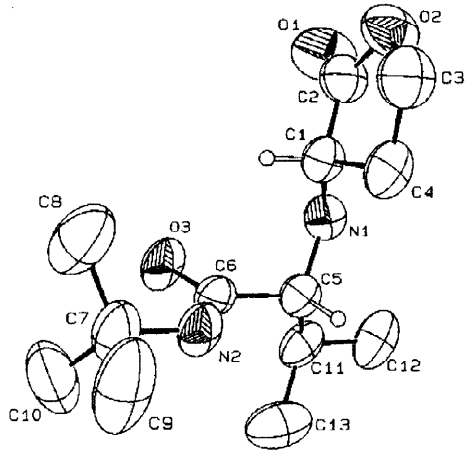


Figure. Molecular structure and selected data for the major stereoisomer of **4b** ($C_{13}H_{24}N_2O_3$, M_r = 256.34) as determined by X-ray analysis: Space group; P1 (No. 1); a = 8.900(2) Å, b = 10.127(5) Å, c = 17.827(3) Å, α = 90.46(3) °, β = 92.18(2) °, γ = 102.70(3) °; V = 1566.1(8) Å^3; Z = 4; μ = 0.077 mm^{-1}; D_{calc} = 1.087 g-cm^{-3}; R1 = 0.0770, wR2 = 0.1888.

In this communication we not only show for the first time a simple one pot synthesis of *N*-carbamoylmethyl-α-aminobutyrolactones **4** *via* the building block approach by the intramolecular Ugi-5-center-3-component reaction (U-5C-3CR) but also considerably extend the scope and effectiveness of the Ugi condensation reaction. This synthesis is characterized as an one pot reaction involving five different functional groups: an aldehyde or ketone, an isocyanide, and homoserine, the latter representing three functional groups combined in one molecule. This intramolecular Ugi condensation reaction will be an excellent tool for a library synthesis of this core structure. The biological activities of the prepared lactones are under examination.

General Experimental Procedure: To 100 mg of L-homoserine **1** (0.84 mmol) in 10 ml of 2,2,2-trifluoroethanol was added 100 M% of the corresponding aldehyde or ketone **2** and the reaction mixture was stirred for 1 or 2 hr. The solution was cooled to 0 °C and then 110 M% of an isocyanide **3** was added. When the reaction was complete at room temperature controlled by the tlc, the solvent was removed in vacuo. The crude mixture was dissolved in 30 ml of methylene choloride and the organic layer was washed with 10 ml of brine solution, and dried over magnesium sulfate. The residue after solvent evaporation was purified by flash column chromatography on silica gel using 1:1 or 1:2 mixture of hexane and ethyl acetate as an eluent.

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