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An Efficient Synthesis of Morpholin-2-one Derivatives Using Glycolaldehyde Dimer by the Ugi Multicomponent Reaction

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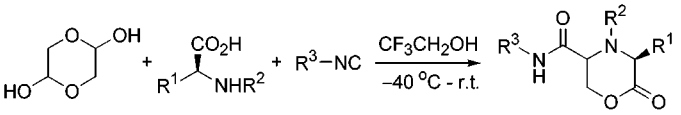
ABSTRACT

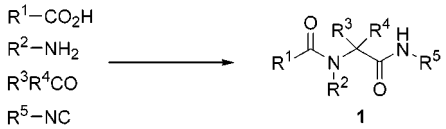


A new one-pot procedure for the efficient synthesis of novel 3-substituted morpholin-2-one-5-carboxamide derivatives using commercially available glycolaldehyde dimer as a bifunctional component with various α-amino acids and isocyanides by the Ugi five-center three-component reaction (U-5C-3CR) was developed.

Recently, multicomponent condensation reactions have become one of the most powerful methods for the synthesis of small molecule libraries, due to the fact that products are formed in a single step by simultaneous reactions of several condensation reagents and the molecular diversity required for such combinatorial libraries can be achieved by simply varying each component.[1]

Especially the Ugi four-component condensation reaction, which combines a carboxylic acid, an amine, a carbonyl compound, and an isocyanide to afford an α-amino amide **1**, has come into widespread use for generating large collections of molecules in combinatorial synthesis (Scheme 1).[2]

Scheme 1. Synthesis of an N-Substituted Acyl Amino Amide **1** from a Carboxylic Acid, a Primary Amine, an Aldehyde or Ketone, and an Isocyanide in a One-Pot Manner



To expand the scope of scaffold diversity generated by this versatile reaction, bifunctional reagents in which the participating functional groups are present in one component have been used to result in construction of various unique structures such as lactams,[3] tetrazoles,[4] imidazoles,[5] pyrroles,[6] diketopiperazines,[7] ketopiperazines,[8] and benzodiazepines.[9]

We were able to also demonstrate that α-amino-butyrolactone derivatives **3** were successfully synthesized by

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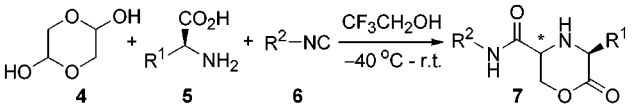
Table 1. Ugi Five-Center Three-Component Reaction of Glycolaldehyde Dimer **4** with Various Isocyanides **5** and α-Amino Acids **6**



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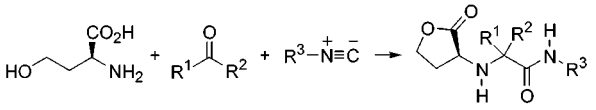
entry	R^1	R^2	time (h)	product	yield (%)[a]	dr[b]	entry	R^1	R^2	time (h)	product	yield (%)[a]	dr[b]
1	$(CH_3)_2CH-$	$(CH_3)_3C-$	24	**7a**	80	1.2:1[c]	9	$PhCH_2-$	EtO_2CCH_2-	48	**7i**	30	1.2:1
2	$(CH_3)_2CH-$	$PhCH_2-$	24	**7b**	88	3.6:1[c]	10	$PhCH_2-$	$TosCH_2-$	48	**7j**	37	3.7:1[c]
3	$(CH_3)_2CH-$	cyclohexyl−	24	**7c**	84	3.6:1	11	CH_3-	$(CH_3)_3C-$	45	**7k**	64	1.8:1
4	$(CH_3)_2CH-$	EtO_2CCH_2-	48	**7d**	58	1.1:1[c]	12	CH_3-	$PhCH_2-$	42	**7l**	64	2.1:1
5	$(CH_3)_2CH-$	$TosCH_2-$	48	**7e**	44	2.0:1[c]	13	$C_2H_5CH(CH_3)-$	$(CH_3)_3C-$	45	**7m**	81	1.7:1
6	$PhCH_2-$	$(CH_3)_3C-$	24	**7f**	90	2.4:1	14	$C_2H_5CH(CH_3)-$	$PhCH_2-$	32	**7n**	65	4.3:1
7	$PhCH_2-$	$PhCH_2-$	24	**7g**	85	2.3:1	15[d]	$CH_3SCH_2CH_2-$	$(CH_3)_3C-$	36	**7o**	63	3.0:1
8	$PhCH_2-$	cyclohexyl−	24	**7h**	78	2.9:1	16[d]	$CH_3SCH_2CH_2-$	$PhCH_2-$	47	**7p**	44	1.6:1

[a] Isolated yields. [b] Diastereomeric ratios were determined by ^1H NMR spectroscopy. [c] Diastereomeric ratios were determined by isolation. [d] D-Amino acid was used.

employing homoserine **2** having three functional groups (an amine, a carboxylic acid, and a hydroxy group) combined in one molecule (Scheme 2).[10]

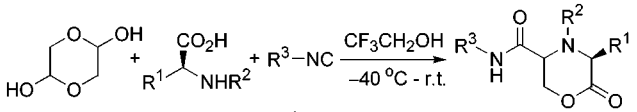
Scheme 2. Synthesis of N-Carbamoylmethyl-α-aminobutyrolactones **3** by the Ugi Five-Center Three-Component Reaction (U-5C-3CR) Using L-Homoserine **2**



2 3

During our extensive work with the Ugi reaction, we found that glycolaldehyde dimer **4** containing an aldehyde functional group and a hydroxy functional group could be a potent bifunctional coupling regent. Despite its versatility, the reactions using glycolaldehyde dimer in the Ugi reaction have never been exploited. We report an efficient synthetic method of novel morpholin-2-one derivatives **7**, a new skeleton in these series, by reacting isocyanides **6** with the bifunctional starting material **4** and α-amino acids **5** (Scheme 3).

Scheme 3. One-Pot Synthesis of the Morpholin-2-one-5-carboxamide Derivatives **7** from Glycolaldehyde Dimer **4**, α-Amino Acids **5**, and Isocyanides **6**



4 5 6 7

The glycolaldehyde dimer **4** was reacted with *tert*-butylisocyanide and L-phenylalanine in 2,2,2-trifluoroethanol at −40 °C, and the mixture was stirred for 1 day at room temperature to afford 3-benzyl-5-*tert*-butylamino carbonyl morpholin-2-one in 90% yield with diastereoselectivity in a ratio of 2.4:1 (Table 1, entry 6). The progress of the reaction largely depends on the experimental procedure. The addition of a premixed solution of an isocyanide and the glycolaldehyde dimer in 2,2,2-trifluoroethanol to the precooled suspension of an α-amino acid in 2,2,2-trifluoroethanol gave the best result, while a typical addition of an isocyanide to the solution of the glycolaldehyde dimer and amino acid was unsuccessful. This reaction did not proceed at all when MeCN or DMF were used as the solvent. When it was run in MeOH or THF in the presence of 1 equiv of $ZnCl_2$, the desired product was isolated in lower yield (65 or 64%), but with better diastereoselectivity (5:1 or 3:1), respectively. Other examples are shown in Table 1.

The reaction of the glycolaldehyde dimer **4** with various α-amino acids **5** and isocyanides **6** provided 3-substituted morpholin-2-one-5-carboxamide derivatives **7** in moderate to good yields. The best observed diastereoselectivity was

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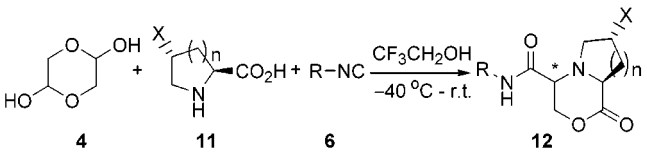
Table 2. Ugi Five-Center-Three-Component Reaction of Glycolaldehyde Dimer **4** with Various Isocyanides **6** and Cyclic α-Amino Acids **11**



4 11 6 12

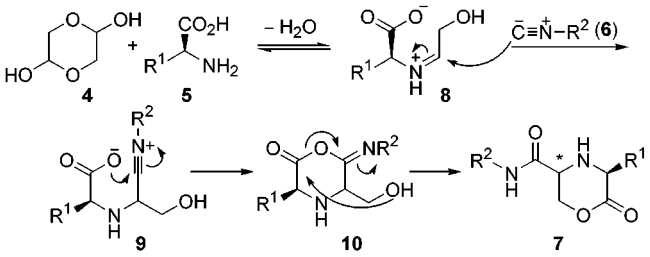
entry	*n*	X	R	time (h)	product	yield (%)[a]	dr[b]	entry	*n*	X	R	time (h)	product	yield (%)[a]	dr[b]
1	0	H	$(CH_3)_3C-$	20	**12a**	58	1.6:1	7	1	OH	$(CH_3)_3C-$	24	**12g**	76	1.8:1
2	0	H	$PhCH_2-$	24	**12b**	74	1.0:1	8[c]	1	OH	$(CH_3)_3C-$	24	**12h**	68	1.7:1
3	1	H	$(CH_3)_3C-$	24	**12c**	87	1.5:1	9	2	H	$(CH_3)_3C-$	24	**12i**	85	2.1:1
4	1	H	$PhCH_2-$	24	**12d**	37	2.8:1	10[d]	2	H	$(CH_3)_3C-$	12	**12j**	84	2.0:1
5	1	H	cyclohexyl−	24	**12e**	79	1.1:1	11[d]	2	H	$PhCH_2-$	12	**12k**	90	1.7:1
6	1	H	EtO_2CCH_2-	48	**12f**	73	2.6:1	12[e]	2		$(CH_3)_3C-$	12	**12l**	77	1.2:1

[a] Isolated yields. [b] Diastereomeric ratios were determined by ^1H NMR spectroscopy. [c] D-Amino acid was used. [d] D,L-Amino acid was used. [e] (*S*)-(−)-1,2,3,4-Tetrahydro-3-isoquinoline-carboxylic acid was used.

4.3:1 (entry 14) by ^1H NMR spectroscopy, where each diastereomer was separated by column chromatography on silica gel.[11]

The mechanism of this reaction is summarized in Scheme 4. The addition of the isocyanide **6** to the prepared imine **8**

Scheme 4. Mechanism of the Ugi Five-Center Three-Component Reaction



4 5 8 9 10 7

gave the intermediate **9**. The interception of the carboxylate on the intermediate nitrilium carbon of **9** followed by the intramolecular hydroxy addition to the carboxylate carbon of **10** resulted in formation of **7**.

When the reaction was carried out in MeOH, the crude product was impure with some ring-opening products, which are formed by the external methanol attack on the carboxylate carbon of the intermediate **10**. Using 2,2,2-trifluoroethanol as a solvent for this reaction was critical in providing the desired product in the view of product purity, reaction rates, and yields.

We were able to demonstrate that glycolaldehyde dimer in the Ugi condensation reaction could be used efficiently

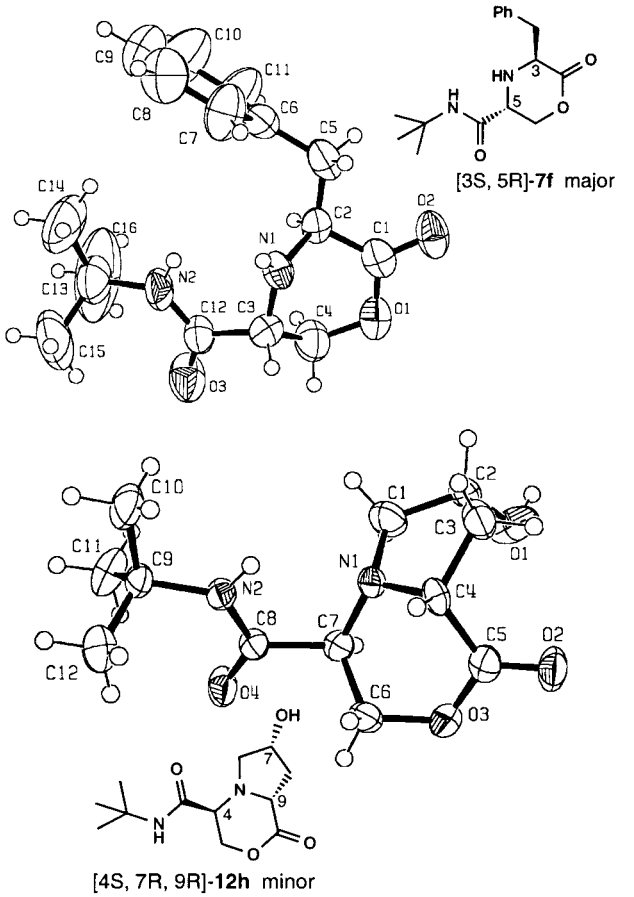


Figure 1. Molecular structures (ORTEP diagrams) for the major isomer of [3*S*,5*R*]-**7f** and minor isomer of [4*S*,7*R*,9*R*]-**12h** as determined by X-ray analysis.

(11) **General experimental procedure**: the solution of a glycolaldehyde dimer **4** (0.4 mmol) and an isocyanide **6** (0.88 mmol) in CF_3CH_2OH (4 mL) was added slowly to a suspension of α-amino acid **5** (0.8 mmol) in CF_3CH_2OH (10 mL) at −40 °C under nitrogen. The mixture was allowed to reach room temperature. After stirring for 24−48 h, the reaction mixture was concentrated under reduced pressure. H_2O (10 mL) and EtOAc (20 mL) were added to the residue, and the resulting aqueous solution was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel with a mixture of hexane and EtOAc (1:1 or 1:2) to give the corresponding morpholin-2-one-5-carboxamide **7**.

to generate chemical diversity in short reaction sequences and to provide libraries of small heterocycles. To the best of our knowledge, only a few morpholin-2-one-5-carboxylic acid derivatives, which cannot be easily prepared by another route, have been communicated.[12] And this method might be the first general and useful synthetic method for the preparation of the morpholin-2-one-5-carboxylic acid derivatives, which represent new cyclic amino acids and cyclic 1,1′-iminodicarboxylic acid derivatives.[13]

To expand the structural diversity accessible through this type of the Ugi five-center three-component reaction (U-5C-3CR), we were able to expand the scope of this reaction by changing the α-amino acid part. When the cyclic amino acids **11** were used, other unique heterobicyclic compounds **12** were produced in moderate to good yields. The results are shown in Table 2.

Compound **7f** and **12h** were characterized by X-ray crystallography (Figure 1).[14] The relative stereochemistry of the major diastereomer **7f** has an R-configuration (3S,5R), and that of the minor isomer of **12h** has an S-configuration (4S,7R,9R) at the newly generated stereogenic carbon C5 and C4 positions, respectively.

In conclusion, by using commercially available glycolaldehyde dimer that has an aldehyde and an alcohol functional group in one component, α-amino acids and isocyanides in a U-5C-3CR, unique morpholine structures were prepared. These new structures broaden the scaffolds that are accessible through the Ugi reactions. The biological activities of the prepared morpholin-2-one derivatives **7** and **12** are now under study.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystal data for the major isomer of **7f**: $M_r = 290.36$, monoclinic, space group *P*2(1) (No. 4), $a = 9.756(2)$ Å, $b = 6.265(3)$ Å, $c = 13.956(4)$ Å, $\alpha = 90.00(3)°$, $\beta = 98.56(2)°$, $\gamma = 90.00(2)°$, $V = 843.5(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.143$ Mg/m^3, $F(000) = 312$, $\mu = 0.079$ mm^{-1}, λ(Mo Kα) = 0.71073 Å, $T = 293(2)$ K, $1.48 < \theta < 24.97$, reflections collected 959, unique 906 ($R_{int} = 0.1383$), observed 906 ($I > 2\sigma(I)$), final R factors $R_1 = 0.0734$, w$R_2 = 0.1801$, GOF = 1.135, parameters refined 190. The absolute configuration at C5 was derived from the known configuration at C3. Crystal data for the minor isomer of **12h**: Mr = 256.30, orthorhombic, space group *P*2(1)2(1)2(1), $a = 9.6199(15)$ Å, b = 11.7608(18) Å, $c = 12.1665(19)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1376.5(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.237$ Mg/m^3, $F(000) = 552$, $\mu = 0.093$ mm^{-1}, λ(Mo Kα) = 0.71073 Å, $T = 233(2)$ K, $2.41 < \theta < 25.52$, reflections collected 7251, unique 2561 ($R_{int} = 0.0532$), observed 2561 ($I > 2\sigma(I)$), final R factors $R_1 = 0.0715$, w$R_2 = 0.1939$, GOF = 0.671, parameters refined 163. A dark orange crystal with approximate dimensions 0.50 × 0.44 × 0.32 mm^3 was selected and attached to the tip of a glass fiber, transferred to a Bruker SMART diffractometer/CCD area detector, and centered under liquid nitrogen in the beam at 233(2) K. The structure was solved using the direct methods from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The absolute configuration at C4 was derived from the known configuration of starting material *cis*-4-hydroxy-D-proline. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-163587 [(3*S*,5*R*)-**7f**] and CCDC-163588 [(4*S*,7*R*,9*R*)-**12h**]. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).