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Liquid-Phase Combinatorial Synthesis of Alicyclic β-Lactams via Ugi Four-Component Reaction

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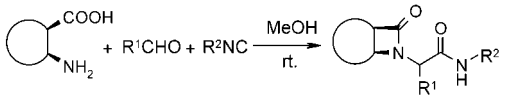
ABSTRACT



Alicyclic β-lactams were successfully synthesized via a parallel liquid-phase Ugi four-center three-component reaction (U-4C-3CR), starting from alicyclic β-amino acids such as *cis*-2-aminocyclohexanecarboxylic acid, *cis*-2-aminocyclopentanecarboxylic acid, 2,3-*diexo*-3-aminobicyclo-[2.2.1]heptane-2-carboxylic acid and some of their partially unsaturated analogues. A six-membered mixture-based combinatorial library of β-lactams was also generated.

Combinatorial chemistry is widely used in pharmaceutical research as a powerful tool for acceleration of the identification of novel therapeutic agents in drug discovery. In this field, multicomponent condensation (MCC) reactions have been utilized very efficiently in conjugation with combinatorial chemistry to prepare large collections of molecules in a short reaction sequence.[1]

One of the most important MCC reactions is the Ugi four-component reaction (U-4CR), in which a carboxylic acid, an amine, a carbonyl compound, and an isocyanide react in a single-stage reaction, affording β-lactam antibiotics and related compounds,[2,3] heterocycles with variable structures such as benzodiazepines,[4] morpholines,[5] tetrazoles,[6] diketopiperazines,[7] and α-aminobutyrolactones.[8]

Some β-lactam derivatives have recently been evaluated as enzyme inhibitors; they exert powerful inhibitory activity against serine protease, elastase (human leucocyte elastase, HLE), cystein protease, and papain. In the past few years, much attention therefore has been paid to the design and synthesis of selective inhibitors for these proteases.[9]

Racemic and enantiopure β-amino acids are of increasing significance in synthetic organic chemistry for the preparation of pharmacologically active heterocyclic natural products.[10,11]

The application of aliphatic β-amino acids in the Ugi reaction, resulting in a monocyclic β-lactam library, has recently been reported. However, the use of cyclic β-amino acids as bifunctional reagents leading to β-lactams does not

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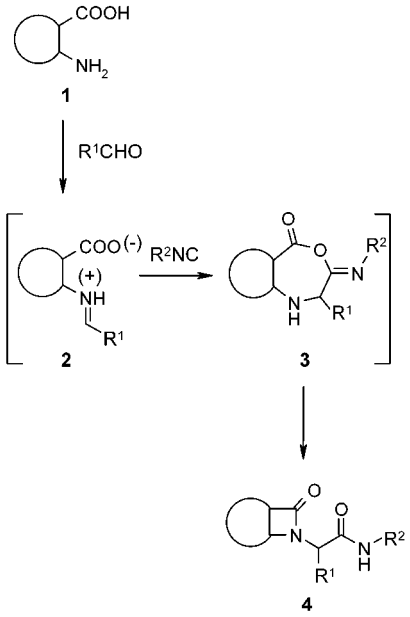
appear to have been exploited.[8] We wish to present here an approach to the parallel liquid-phase synthesis of β-lactams, utilizing cyclic β-amino acids in an Ugi four-center three-component reaction (U-4C-3CR), and we illustrate the use of this approach to create a small mixture-based library.

The general reaction is represented in Scheme 1. Starting from cyclic β-amino acid **1**, which supplies the carboxylic acid and the amino function, azetidinone ring **4** is formed in the U-4C-3CR (Scheme 1). In the first step, reaction with the aldehyde affords protonated Schiff's base **2**, which then reacts with the isocyanide, affording oxazepinone **3**. The latter undergoes in situ O,N-acyl migration, resulting in β-lactam **4**.[12]

Scheme 1. Formation of Azetidinone Ring **4** from Cyclic β-Amino Acid **1**



The U-4C-3CR was investigated by using the racemic cyclic β-amino acids **1a**−**g** represented in Figure 1.[13] In the reactions of *trans*-2-aminocyclohexane- and *trans*-2-aminocyclopentanecarboxylic acids **1b** and **1d** with 4-nitrobenzaldehyde and cyclohexyl isocyanide in MeOH, no cyclized products were formed after 24 h, either at room temperature or at 60 °C. The *trans*-amino acids failed to cyclize because the magnitude of the ring strain prevents the formation of a *trans* β-lactam. On the other hand, under the same conditions *cis*-2-aminocyclohexanecarboxylic acid **1a** was smoothly transformed into the β-lactam. For this reason, the *cis* β-amino acids were selected for further investigations. To compare the reactivities of *cis* β-amino acids in the Ugi reaction, *cis*-2-aminocyclohexane-, *cis*-2-aminocyclopentane-, and *cis*-2-aminocyclohex-4-enecarboxylic acid (**1a**, **1c**, and **1e**) and 3-*exo*-aminobicyclo[2.2.1]heptane-2-*exo*- and 3-*exo*-aminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (**1g** and **1f**) were reacted with cyclohexyl isocyanide and 4-nitrobenzaldehyde in parallel syntheses by stirring the mixtures in MeOH at room temperature (Figure 2).

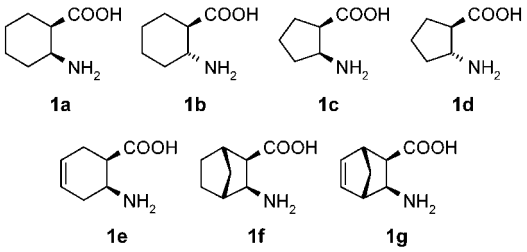


Figure 1. Cyclic β-amino acids **1a**−**g** utilized in the U-4C-3CR.

Most of the reactions were complete within 24 h, resulting in the β-lactam derivatives **4a**−**e** in moderate to good yields after separation. Upon the application of other aromatic aldehydes, such as 2-pyridinecarboxaldehyde, 3-chlorobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, and formaldehyde, in the Ugi reaction, β-lactams **4f**−**i** were isolated in only moderate yields after separation.

In all cases except **4i** (R^1 = H), the U-4C-3CR leads to the formation of a new stereogenic center at position C2 of the acetamido group in the final product. In the crude reaction mixtures, the diastereoisomeric ratio varies from 4:3 to 10:1. After column chromatography, in most cases the major isomer was obtained in pure form, with the exceptions of compounds **4b**, **4e**, and **4g**.

Acid-catalyzed solvolysis of the azetidinone ring in the case of compound **4c** was also carried out in the presence of water or EtOH, resulting in the corresponding carboxylic acid **5** or the ethyl ester **6**, respectively (Scheme 2).

Since the bicyclic β-lactams were obtained in moderate to good yields in the parallel syntheses, we decided to synthesize a small mixture-based β-lactam library (**11a**−**f**)

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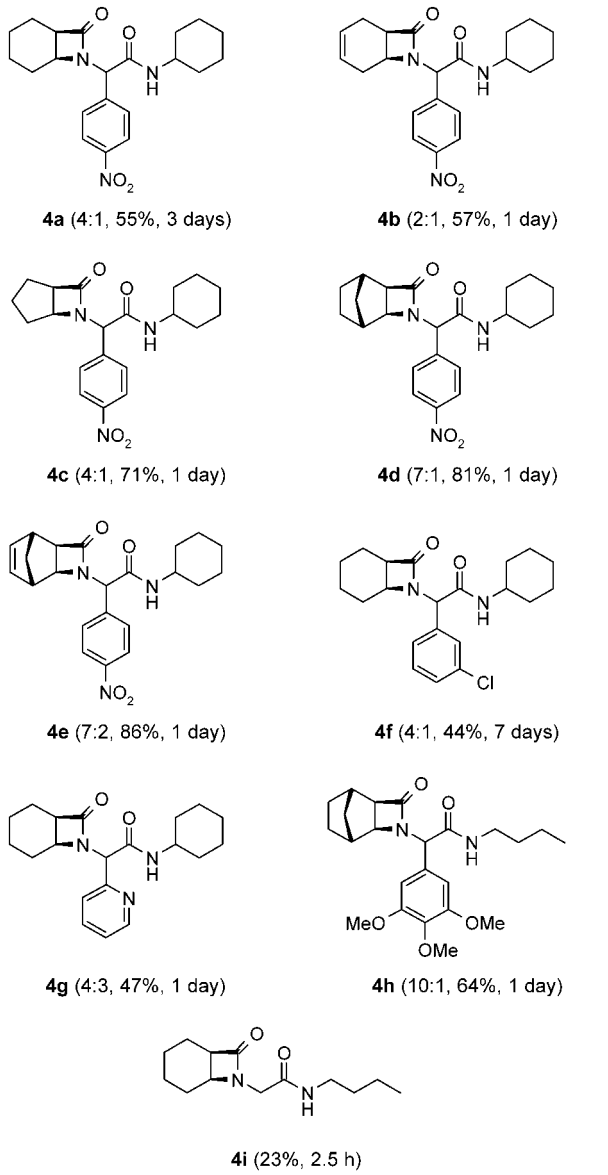

Figure 2. Isomeric ratio of crude products, yields of purified products, and reaction times in syntheses of β-lactam derivatives in the parallel liquid-phase Ugi reaction.

by the above method.[14] Figure 3 shows the building blocks of a six-membered library, which was created in a one-pot reaction by combining two β-amino acids, **1a** and **1c**, three different aldehydes, **8**−**10**, and cyclohexyl isocyanide **7**.

The solution-phase library was prepared in MeOH by stirring the mixture at room temperature for 3 days. The library was purified by column chromatography. The accurate masses of the purified library components were measured by MS-MS, with detection of their protonated molecular ions ($M + H^+$). This confirmed our expectation that all of the components were present in the mixture.

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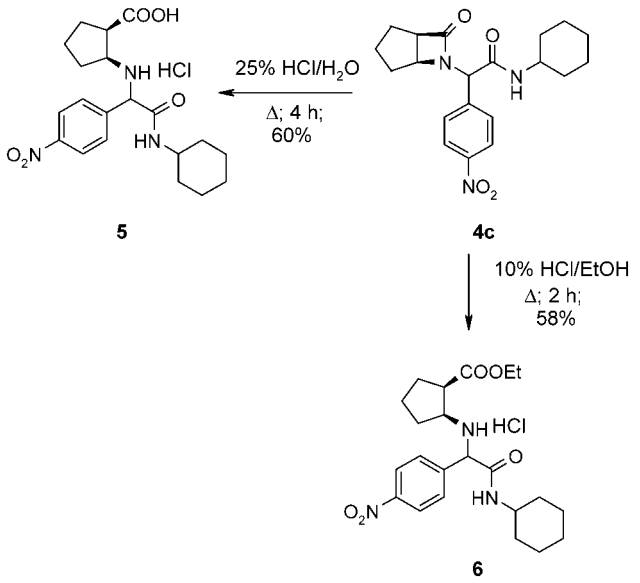
Scheme 2



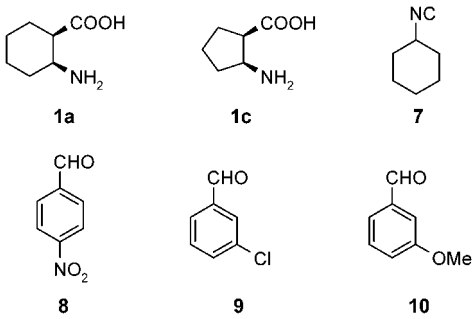


Figure 3. Building blocks of the 1 × 2 × 3-membered mixture-based Ugi library.

In conclusion, we found that the U-4C-3CR is an efficient method with which to prepare *cis* β-lactam derivatives **4a**−**i** by reacting an alicyclic *cis* β-amino acid, an aldehyde, and an isocyanide. By the above method, a small mixture-based β-lactam library was created in the liquid phase, with three points of diversity, containing 1 × 2 × 3 components.

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

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