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Stereoselective Synthesis of Quaternary Pyrrolidine-2,3-diones and β -Amino Acids

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Abstract

A facile, diastereoselective synthesis of highly substituted pyrrolidine-2,3-diones is reported, along with the one-step conversion of these heterocycles to novel β -amino acids and further functionalized derivatives. This method involves an unusually mild, one-pot, three-component cyclization/allylation followed by a Claisen rearrangement to provide unusual pyrrolidinone products that are densely functionalized and contain an all-carbon quaternary stereocenter. The reported reaction sequence is operationally simple, exquisitely diastereoselective, and provides gram-scale access to valuable heterocyclic scaffolds and β -amino acids not readily accessible via existing approaches.

Graphical abstract

Nitrogen-containing heterocycles are common core scaffolds in natural products and pharmaceutical agents. In particular, five-membered nitrogen-containing heterocycles are among the most prevalent motifs in bioactive molecules and represent a key synthetic hurdle for their facile synthesis (Figure 1a). Among the many synthetic approaches to *N*-heterocycles, the use of multicomponent reactions (MCRs) is a powerful tool to access diversity of substitution in relatively short reaction sequences.¹ In addition to step economy, a particularly appealing feature of MCRs is the rapid generation of structural diversity

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures; characterization of products; ¹H and ¹³C NMR spectra (PDF)

X-ray crystallographic data for compound **13b** (CIF)

X-ray crystallographic data for compound **19d** (CIF)

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through the utilization of a secondary transformation of the obtained scaffolds. The increasing power of multicomponent and cascade reactions can be observed in natural product synthesis, where bond-forming processes are merged more frequently to achieve molecular complexity.²

Multicomponent reactions of readily enolizable carbonyls with various amines and aldehydes (for example, Mannich- and Doebner-type reactions), supplemented by docking studies and high-throughput screening approaches, have enabled the discovery of functionalized and bioactive pyrrolone^{3a} and quinoline⁴ heterocycles. In particular, 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones (**4**) have attracted much attention due to their wide spectrum of biological activities such as anticancer,⁵ antimicrobial,⁶ antiviral,^{3b} and protein–protein interaction inhibitors.^{7a,b} A variety of combinatorial libraries of heterocycles with general structure **4** have been prepared via multicomponent approaches (Figure 1b) employing substituted α -oxo esters/acids (**1**), aldehydes (**2**), and amines (**3**).^{7–9} Typical conditions involve polar solvents such as dioxane, THF, or EtOH with less reactive amine substrates heated in AcOH or DMF in the presence of TMSCl; unfortunately, aliphatic aldehydes are scarcely employed and usually provide low yields of pyrrolone products.^{5a,7–10} An alternate multicomponent approach¹¹ as well as asymmetric protocols for the synthesis of 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones were also recently described.¹² In this work, we investigated 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones as high-value building blocks for more densely functionalized heterocycles and natural products and therefore sought optimized methods for their preparation.

We recently reported the first total synthesis of the antimicrobial natural products synoxazolidinones A and B via an imine acylation/cyclization cascade as a key transformation to install the 4-oxazolidinone core.¹³ In this method, acylation of *N*-dimethoxybenzylimines derived from aliphatic aldehydes with arylpyruvic acid chlorides provided 4-oxazolidinone products exclusively, albeit in moderate yields (Table 1, entries 1 and 2). In attempts to improve the efficiency of the cyclization to obtain 4-oxazolidinones, we explored various activated derivatives of phenylpyruvic acid and identified regioisomeric 1,5-dihydropyrrol-2-one products under these alternate conditions (Table 1, entries 3–5).¹³ Given the importance of dihydropyrrolones in medicinal chemistry and our interest in developing these scaffolds as building blocks, we desired to further explore these reactions with the aim of overcoming previous limitations in substrate scope and functional group compatibility.

Although our initial studies focused on activated carboxylic acid derivatives, full conversion was observed when methyl ester **6** was treated with preformed imine **7** (Table 1, entry 6); however, varied amounts of dihydropyrrolone product were isolated after chromatography, pointing to the instability of **9** to SiO₂. Similarly, Guo et al. observed lowered yields of *N*-tosyl 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones after purification.¹² To circumvent the product decomposition, the enol moiety of **9** was protected as a silyl ether (Table 1, entry 7), which allowed for isolation of the desired product in 92% yield.

At this stage, we sought to avoid preformation of the imines as well as the need for column purification and therefore explored the one-pot reaction of the amine, aldehyde, and ester.

Gratifyingly, when imine **7** was formed in the presence of the ester in acetonitrile (Table 1, entries 8–10), the desired dihydropyrrol-2-ones precipitated from the reaction mixture and were isolated by filtration in high yields and excellent purity. Attempts to remove water (MgSO₄, sieves, etc.) during the reaction led to lower yields and byproduct formation. Notably, the reactions are extremely rapid and likely proceed via an initial acid–base reaction between the enol and basic imine, addition of the resulting enolate to the iminium ion, and subsequent ring closure and loss of methanol. The lack of an additional activating carbonyl on the pyruvate fragment, the mild nature of these reactions and the use of electron-rich and aliphatic imines make this process distinct from existing MCRs toward this substrate class.^{7–12}

With a high-yielding, three-component reaction to form our target heterocycle in hand, we planned to leverage these scaffolds as building blocks for more functionalized molecules. Synthetic transformations of 1,5-dihydro-2*H*-pyrrol-2-ones¹⁴ have previously provided entry to other complex structures such as α -keto γ -lactams,^{15a} natural products,^{15b} and related biologically active small molecules.¹⁶ Interestingly, rearrangement reactions of 1,5-dihydro-2*H*-pyrrol-2-ones remain largely underexplored yet would provide a significant increase in molecular complexity and access to quaternary substituted heterocycles.^{14,17} To explore the potential of this approach, we proposed the allylation of 1,5-dihydro-2*H*-pyrrol-2-one products (**11**) and optimized a two-step, one-pot protocol for the synthesis of 3-(allyloxy)-1,5-dihydro-2*H*-pyrrol-2-ones (**12**, Scheme 1). Allylated derivatives **12a–o** were readily prepared in moderate to high yields, allowing rapid access to aryl-, alkenyl-, and alkyl-substituted compounds not easily accessible (Scheme 1).

To explore the potential of 3-(allyloxy)-1,5-dihydro-2*H*-pyrrol-2-ones (**12**) as substrates for sigmatropic rearrangements, we heated **12b** at reflux overnight in toluene and observed full conversion to 4-allylpyrrolidine-2,3-dione **13b** and isolated the product in quantitative yield following removal of the solvent (Scheme 2). Importantly, the reaction proceeded in a highly diastereoselective fashion providing only one observed diastereomer. The preference of the allyl moiety to approach from the least hindered face, opposite to the substituent at C5, was confirmed by X-ray analysis of **13b**. It should be noted that under thermal conditions the rearrangement proceeded slowly with an average reaction time of 12–18 h. Other pyrrolidine-2,3-diones (except **13j**) were also obtained quantitatively after evaporation of toluene and no purification was required. Thermal rearrangement of substrate **12j** bearing an alkenyl moiety proceeded with a color change to deep green even at lower temperatures, accompanied by low yields of product **13j** (10–18%) following purification. This prompted us to explore an alternate, Pd-catalyzed Tsuji–Trost allylation of 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones as a rapid strategy to form pyrrolidine-2,3-diones containing a quaternary stereocenter in cases where thermal rearrangement was not feasible.¹⁸ Standard conditions of Tsuji–Trost type allylation (Pd–allyl dimer catalyst, P-ligand, and base) applied toward **11j** proceeded at 0 °C, and full conversion was achieved in 30 min resulting in 93% yield of **13j** (same relative stereochemistry observed in Claisen rearrangement, confirmed by NMR).^{19,20} Pyrrolone **13h** could also be isolated as a single diastereomer in 95% yield after isolation and purification via this approach.

The 4-allylpyrrolidine-2,3-dione products **13a–o** possess a novel dione-substituted heterocyclic core and share structural similarity with isatins, a class of privileged scaffolds²¹ contained in natural products and drug candidates.²² Previous extensive exploration into the reactivity of isatins (nucleophilic addition to C3 carbonyl, oxidations, spiro-annulations, etc.) has provided useful insights into the potential reactivity of pyrrolidine-2,3-diones, albeit the isatin scaffold bears a fused aromatic ring.^{22c} We explored ring modifications of the pyrrolidine-2,3-dione products to evaluate the potential to further functionalize these scaffolds. Our preliminary investigations were centered around functionalization of the alkene and ketone groups (Scheme 3). Initially, to take advantage of the alkenes already present in substrate **13a**, seven-membered alkene **14** was prepared via ring-closing metathesis (RCM) in good yield by employing the first-generation Grubbs' catalyst. Incorporation of an additional allyl moiety was also explored, and addition of allylmagnesium bromide to **15d** followed by RCM provided bicyclic γ -lactams **16** and **17** in 67% yield (Scheme 3).

We further envisioned exploration of ring opening reactions of 4-allylpyrrolidine-2,3-diones for the synthesis of novel $\beta^{2,2,3}$ -amino acids (Scheme 4). A multitude of methods exist for the synthesis of monosubstituted β -amino acids at the β^2 and/or β^3 positions;²³ however, only few reports describe the preparation of disubstituted $\beta^{2,2}$ - or $\beta^{3,3}$ -derivatives as this substitution pattern requires the synthetically challenging formation of a quaternary stereocenter.²⁴ In most cases, limitations in the synthesis of the starting materials lead to a lack of versatility in the achievable substitution pattern. Given the considerable chemical and biological potential of β -amino acids, the development of rapid and scalable approaches to access their novel derivatives is of high importance.

A demonstration of the conversion of commercially available materials to complex, quaternary-substituted β -amino acids is shown in Scheme 4. The three-component reaction of methyl ester, aldehyde, and 2,4-dimethoxybenzylamine (2,4-DMBA) afforded 1,5-dihydro-2*H*-pyrrol-2-ones **11b,d,h** which were isolated by filtration. One-pot allylation with allyl bromide followed by removal of dimethoxybenzyl substituent using TFA in DCM (1:1 v/v) furnished allyl vinyl ethers **15b,d,h** in good yields; importantly, gram quantities of products could be obtained. Claisen rearrangement in refluxing toluene followed by purification provided 4-allylpyrrolidine-2,3-dione **18b,d,h** as single diastereomers. At this stage, the separation of enantiomers could be achieved by conversion of **18d** to ketimine diastereomers followed by column separation and removal of chiral auxiliary (see the Supporting Information) if desired. Oxidative ring opening of the pyrrolidine-2,3-dione was achieved by treatment of **18b,d,h** with 1 M NaOH and 30% hydrogen peroxide to furnish β -amino acids **19b,d,h**, which could be isolated by filtration after acidic work up or easily purified by reversed-phase flash chromatography. Slow evaporation from wet methanol allowed for crystallization of **19d**, the structure of which was confirmed by X-ray analysis (Scheme 4). In addition, **19d** was readily converted to the corresponding β -lactam **20d** in good yield, highlighting one potential application of the β -amino acids.

In summary, we have optimized a protocol for the preparation of alkyl-substituted 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones in high yield. Subsequent Claisen rearrangement of allyl ether derivatives of these heterocycles enabled access to novel pyrrolidine-2,3-dione

heterocycles containing a quaternary stereocenter. We have demonstrated that straightforward transformations of pyrrolidine-2,3-diones at the alkene and ketone moieties can provide rapid access to *N*-containing polycyclic scaffolds. Importantly, we found that 4-allylpyrrolidine-2,3-diones could be converted to $\beta^{2,2,3}$ -amino acids via oxidative ring opening. A variety of other complexity-building transformations (cycloadditions, reduction to amino alcohols, etc.) can be envisioned to build in complexity around the pyrrolidine-2,3-dione core, and efforts to explore these transformations as well as the rendering of our key three-component reaction asymmetric are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Representative natural product and medicinally relevant heterocyclic scaffolds. (b) Current approaches to 3-hydroxy-1,5-dihydropyrrol-2-ones via multicomponent (left) and two-step protocols (right).

R₁=Ph, R₂:

2 step yields

R₂=C₅H₁₁, R₁:

Scheme 1.

Substrate Scope of 3-(Allyloxy)-1,5-dihydro-2H-pyrrol-2-one Synthesis

Scheme 2.

Synthesis of Novel Pyrrolidine-2,3-dione Heterocycles Containing All-Carbon Quaternary Stereocenter^a

^aReaction conditions: (a) toluene, 110 °C, quantitative yield; (b) 5 mol % (Pd η^3 C₃H₅Cl)₂, *R*-(+)-BINAP, 10 mol %, *t*BuOK, allylOAc, toluene, 0 °C to rt, 30 min, **13h** (95%) and **13j** (93%).

I. Synthesis of cyclic alkenes:

II. Synthesis of bicyclic γ -lactams:

Scheme 3.

Conversion of 4-Allylpyrrolidine-2,3-diones to Cyclic Alkene Derivatives via Ring-Closing Metathesis Reactions

Scheme 4. Synthesis of Novel $\beta^{2,2,3}$ -Amino Acids and β -Lactam Derivatives

Table 1

Reaction Optimization: Synthesis of Alkyl-Containing Dihydropyrrolones

entry	X	R	conditions	yield ^a (%)	
				8	9
1	-OH	C ₅ H ₁₁	(COCl) ₂ , cat. DMF, THF/CH ₂ Cl ₂ , 0 °C	17–40 ^b	
2	-OH	C ₅ H ₁₁	PyBOP, DIPEA, THF/CH ₂ Cl ₂ , 0 °C	24 ^b	
3	-OH	C ₅ H ₁₁	DCC, DMAP; CH ₂ Cl ₂ , 0 °C		6 ^b
4	-OH	C ₅ H ₁₁	(CNCl) ₃ , Et ₃ N, MeCN, 0 °C	7 ^b	40 ^b
5	-OH	C ₅ H ₁₁	MeCN, 0 °C		10 ^b
6	-OMe	C ₅ H ₁₁	CH ₂ Cl ₂ , 0 °C		60 ^b
7	-OMe	C ₅ H ₁₁	CH ₂ Cl ₂ , 0 °C; TBSCl, imidazole		92 ^{c,d}
8	-OMe	C ₄ H ₉	MeCN, 0 °C		83 ^e
9	-OMe	dPr	MeCN, 0 °C		78 ^e
10	-OMe	Ph	MeCN, 0 °C		71 ^e

^a Isolated yield.^b 7 was preformed (2,4-DMBA with aldehyde in the presence of MgSO₄).^c Aldehyde and 2,4-DMBA were added to a solution of ester in CH₂Cl₂ without MgSO₄.^d 3-OH of 9 was protected with TBDMS prior to purification.^e Isolated by filtration.