Final report

Title: The synthetic study of the aza-annulation reaction of enamines and further decarboxylative modifications

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Abstract

Aza-annulation of enamines generated from β-ketoester using maleic and itaconic anhydrides produces functionalized γ- and δ-lactams with good diastereoselectivity. Subsequent hydrolysis of the aza-annulation products yielded dicarboxylic acids, which are susceptible to further decarboxylation. Simultaneous migration of the C=C double bond occurs during the decarboxylation of β-γ unsaturated carboxylic acids with an electron-rich enamide double bond. This provides a straightforward synthesis route towards 1,2,3,4-tetrahydropyridine-2-ones and 3-pyrrolin-2-ones.

Keywords

Aza-annulation, regioselectivity, stereoselectivity, decarboxylation.

Introduction

Pharma product design benefits greatly from the use of nitrogen heterocycles. Nitrogen heterocycles are present in 59% of small-molecule medications, according to research by Vitaku E. et al. Specifically, the most common structure classes among the five-membered (14.7%) and six-membered (19.0%) N-heterocycles are the pyrrolidine and piperidine structure classes.[1]

Particular attention should be paid to five- and six-membered lactams among nitrogen heterocycles.[2] Nowadays, medications for Alzheimer's disease, PTSD, and depression are prescribed that contain derivatives of pyrrolidone.[3] 2-Piperidinone base scaffolds have therapeutic applications as well; at the moment, their anti-tumorous, anti-HIV, and enzyme inhibition properties have drawn attention.[4] Moreover, because of their three-dimensional nature, spirocyclic N-heterocycles have higher physicochemical qualities than analogous monocyclic scaffolds.[5] Functionalized γ-lactams and δ-lactams (including spirocyclic forms) exhibit great promise in medicinal chemistry, as demonstrated. As a result, a practical, scalable, affordable, enantio- and diastereoselective synthesis technique is needed.

Numerous techniques for synthesizing functionalized γ-lactams and δ-lactams are currently available. Despite their apparent simplicity, the synthetic pathways leading to partially unsaturated 2-pyrrolidone and 2-piperidine cores involve complex multistep transformations of suitable starting materials,[6] involve the use of transition-metal-catalyzed ring-closing metathesis,[7] α-selenation-elimination sequence,[8] pyrrole oxidation,[9] and transition-metal-catalyzed cross-couplings.[6-10]

However, the primary benefits of the aza-annulation reaction are its stereoselectivity, simple process, functionalized produced scaffolds, and the fact that it does not require the use of hazardous substances or catalysts. Furthermore, the aza-annulation methodology is not limited to the synthesis of five- and six-membered lactams. For example, a remarkable synthesis of libraries based on an aza-annulation reaction was described by Kozmin et al. in 2012. 1872 compounds were produced in a variety of heterocyclic libraries by virtue of the automatized amide coupling.[11] Subsequently, it is discovered that the yielded compounds can be easily decorated with different functionalities.[12]

We envisaged the aza-annulation of 2-ketoester-derived enamines followed by the hydrolysis and decarboxylation of the resulting products as a reliable synthetic pathway to unsaturated 2-pyrrolidones and 2-piperidineones. This record describes our findings.

Experimental procedures

The general procedure for the enamine synthesis is a condensation reaction of the chosen ketoester with different amines in chloroform following the standard workup process.

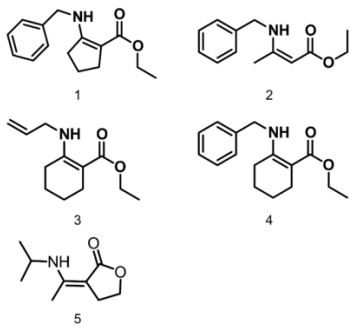


Figure 1. The scope of stating materials (enamines).

The general procedure for aza-annulation is an addition of maleic or itaconic anhydride to the enamine obtained in the former step with chloroform used as a solvent at room temperature. Since it is an addition reaction and no byproducts are formed, no workup besides solvent evaporation is required.

The general procedure for decarboxylation was optimized in the laboratory and consisted of two sequential one-pot reactions. The first reaction is the saponification aza-annulation product with sodium hydroxide in ethanol/DI water solvent. Next, decarboxylation was achieved by evaporating ethanol from the reaction mixture, quenching with DI water adding a strong mineral acid – 10% sulfuric acid and heating under reflux. Then, a general workup procedure is performed.

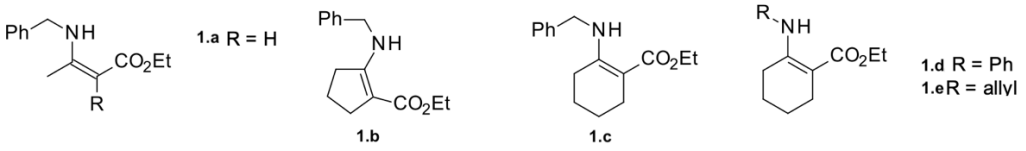
In cases when aza-annulation products need to be purified recrystallization or esterification followed by column chromatography is performed. Esterification of the aza-annulation products was performed under the following conditions: potassium sulfate, and iodomethane at room temperature in DMF.

Techniques used to purify and characterize products: thin layer chromatography, column chromatography, recrystallization, ^{1}H, ^{13}C NMR spectroscopy, and GC/MS analysis.

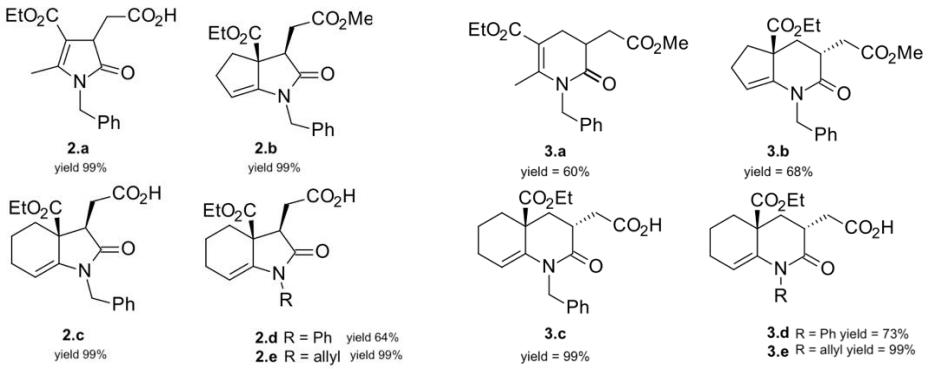
Results and Discussion

In order to test our idea, we first synthesized a range of aza-annulation products by treating the enamines that resulted from treating basic ketoesters with primary amines to get enamines (Scheme 1); and subsequently with itaconic and maleic anhydrides (Scheme 2). exceptional diastereoselectivity and good to exceptional yields of functionalized γ- and δ-lactams were achieved. The previous report for Directed Research I contains a full synthesis report and assessment of the aza-annulation products. ^{1}H, ^{13}C NMR spectra that showcased their purity and yields, and spectra found in literature supported our deduced structures. We then looked into the possibility of decarboxylation of the dicarboxylic acids obtained by saponification of the aza-annulation products.

In the previous report, we mentioned that only three of 5 intended enamines were obtained thus the synthetic strategy examination was limited to only 3 cases. In this research period, we achieved the initially intended scope and now present results for this extended scope and suggest a decarboxylation mechanism supported by the ^{1}H NMR experiment.



Scheme 1. Enamines used.



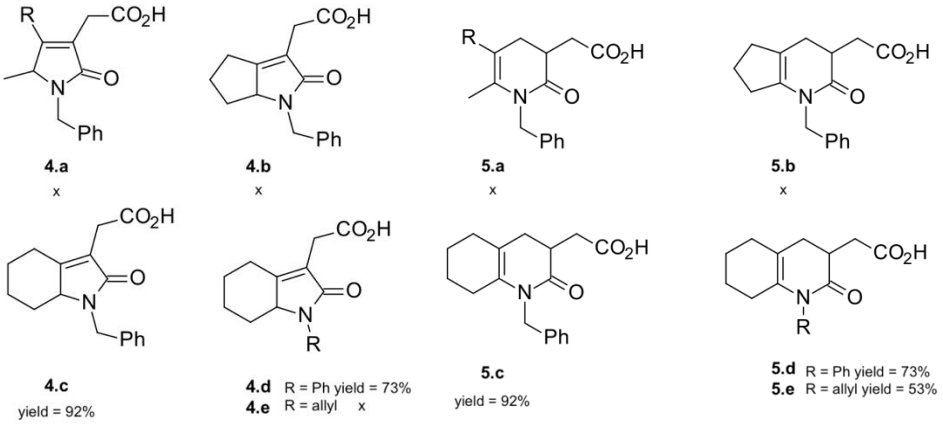
Scheme 2. Aza-annulation products obtained from enamines (number 2- with maleic, number 3 – with itaconic anhydrides).

Following the saponification of aza-annulation products 2 and 3, we looked into the possibility of decarboxylation of the dicarboxylic acids. As a result, attempts to hydrolyze 2a under basic circumstances produced complex reaction mixtures, but under moderately severe conditions, the dicarboxylic acid extracted from 3a did not decarboxylate (as reported in Directed study I). However, because of partial decarboxylation, hydrolyzed 2C and 3C seemed unstable in an acidic workup at room temperature. On the other hand, the deprotonated form of these dicarboxylic acids does not exhibit any appreciable modifications upon storage.

Refluxing the protonated forms of hydrolyzed 2c and 3c in acidic aqueous solutions for a brief duration (10–30 minutes) produced the best results. The NMR findings presented compelling evidence of the creation of 1,2,3,4-tetrahydropyridine-2-one (5c) and 3-pyrrolin-2-one (4c) complexes due to C=C double bond migration and CO2 loss. The crucial factor for the decarboxylation reaction is therefore the placement of the exocyclic enamide β-C=C double bond in the aza-annulation product (2a vs. 2c and 3a vs. 3c).

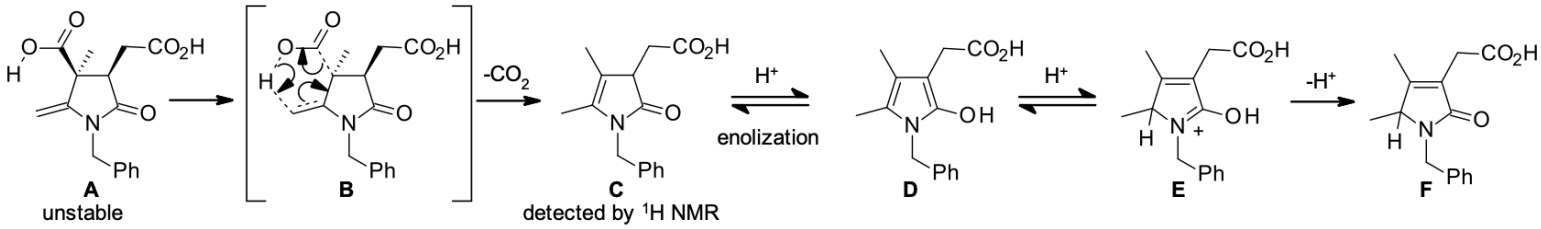
We began investigating the reaction's potential and limitations after obtaining working reaction conditions and the established structures of the decarboxylation products. After treating the aza-annulation products 2c,d with NaOH in aqueous ethanol to guarantee full ester functional group hydrolysis, 3-pyrrolin-2-ones 4c,d were produced in good to excellent yields by acidifying with diluted H2SO4 and refluxing for 10–30 minutes. Remarkably, most of the time no further purification was needed.

Surprisingly, under the decarboxylation circumstances, lactams 2b and 2e produced a complicated combination of unknown chemicals.
To obtain good to exceptional yields of the decarboxylation products 5c-e, the series of aza-annulation products 3b-e were subjected to similar reaction conditions. With the exception of 5b, all cases had no problems and produced moderate to good yields of the decarboxylation products. A different strategy for decarboxylation was created for the chemicals that might be sensitive to acid. In order to achieve complete and clean decarboxylation with a 56% overall isolated yield, the hydrolyzed aza-annulation product 3b can be treated with citric acid to ensure mild acidification. After that, the dicarboxylic acid is extracted using a suitable organic solvent, and the solution is kept overnight at room temperature.



Scheme 3. Decarboxylation products obtained (number 4 – from aza-annulation products 2, number 3 – from aza-annulation products 3).

For simple β-γ-unsaturated carboxylic acids to undergo thermal decarboxylation, severe criteria must be met, including the simultaneous migration of the C=C double bond and a likely 6-membered ring transition state (19–22).23, 24 Furthermore, it was demonstrated that the decarboxylation rate is accelerated by substituents at the C=C bond that donate electrons.24 A tenable route for the decarboxylation of the hydrolyzed aza-annulation products can be suggested in light of the results that have been presented. After the 5-membered lactam is hydrolyzed and then protonated with an exocyclic double bond, unstable dicarboxylic acid A is produced. This acid is then decarboxylated through a 6-membered cyclic transition state B, resulting in 1,3-dihydropyrrol-2-one C, which was identified using 1H NMR. The latter isomerizes via several protonation-deprotonation stages, including D and E, to stable 1,5-dihydropyrrol-2-one F (Scheme 2c). For δ-lactams 6b-j, reversible aromatization cannot facilitate the migration of the C=C bond, resulting in the final products of the decarboxylation reaction being 1,2,3,4-tetrahydropyridine-2-ones.



Scheme 5. Proposed mechanism of decarboxylation.

Conclusion

Ultimately, 3-pyrrolyn-2-ones and 1,2,3,4-tetrahydropyridine-2-ones are produced by the decarboxylation of aza-annulation products. Electron-rich β-γ-unsaturated carboxylic acid structural motif allows for effortless decarboxylation facilitates electron transfer within the 6-membered ring transition state and concurrently is responsible for C=C bond migration.

Acknowledgments

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P.S.: I didn't have a laptop on Windows with drawing software, so the schemes look bad.

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