

# Synthesis of a $\gamma$ -Lactam Library via Formal Cycloaddition of Imines and Substituted Succinic Anhydrides

Darlene Q. Tan, Amy L. Atherton, Austin J. Smith, Cristian Soldi, Katherine A. Hurley, James C. Fettinger, and Jared T. Shaw\*

Department of Chemistry, One Shields Ave, University of California, Davis, California 95616, United States

**Supporting Information** 

**ABSTRACT:** Formal cycloaddition reactions between imines and cyclic anhydrides serve as starting point for the synthesis of diverse libraries of small molecules. The synthesis of succinic anhydrides substituted with electron-withdrawing groups is facilitated by new mild conditions for alkylation of aryl-substituted acetyl esters with ethyl bromoacetate. These anhydrides are then used in formal cycloaddition reactions with imines to produce  $\gamma$ -lactams. 2-Fluoro-5-nitrophenylsuccinic anhydride reacts effi-



ciently with imines to provide lactams that are further diversified by conversion of the nitro group to either an aniline and an azide for subsequent reactions with acylating agents and alkynes, respectively. The synthesis of cyanosuccinic anhydride is reported for the first time, and the use of this compound in reactions with imines and subsequent functionalization of the resultant lactams is demonstrated.

**KEYWORDS**: *imine-anhydride formal cycloaddition, cyanosuccinic anhydrides,*  $\gamma$ *-lactams, spirooxindole* 

# INTRODUCTION

 $\gamma$ -Lactams represent important substructures for the synthesis of natural products<sup>1–5</sup> and biologically important compounds in drug discovery.<sup>6–9</sup> In addition, spirobicyclic lactams are also found in a number of biologically active natural products.<sup>10–12</sup> The prevalence of these structures has resulted in the development of many efficient syntheses,<sup>13–18</sup> which have led to the production of diverse libraries of small molecules for biological evaluation.<sup>9,19,20</sup>

Previous work in our laboratory has employed the formal cycloaddition reaction of imines and anhydrides<sup>13,21,22</sup> in the synthesis of a diverse collection of polycyclic lactams using solid-phase, split-pool synthesis.9 A portion of that library resulted from imine-anhydride reactions of substituted phenylsuccinic anhydrides.<sup>23</sup> As part of that study, we documented the superior reactivity of phenylsuccinic anhydrides that were substituted with electron-withdrawing groups, which we believe emanates from increased enolate stabilization of the cyclization intermediate. As a complement to those investigations, we wanted to develop solution-based strategies for the preparation of these complex molecules for high-throughput screening studies after purification by preparative HPLC. In addition, we wanted syntheses that were amenable to immediate execution on larger scale for follow-up studies, establishment of structureactivity relationships, and other experiments necessary for optimizing potency and selectivity against a biological target.

We selected three different substituted succinic anhydrides to demonstrate the utility of the imine-anhydride reaction in library synthesis (Figure 1). One liability associated with the substituted succinic anhydrides emanates from difficulties in their preparation, thus limiting the structural diversity of compounds made from this reaction. We set out to develop better conditions for preparing substituted succinic anhydrides. 2-Fluoro-5-nitrophenylsuccinic anhydride (2a) allows for a variety of subsequent transformations, including the formation of spirooxindoles. Cyanosuccinic anhydride (2b) was unknown in the literature at the outset of our studies and was anticipated to require much shorter reaction times than previously observed in the imine-anhydride reaction. 2-Benzothiazolesuccinic anhydride (2c) would install a heterocycle on the 4-position of the lactam, which has not previously been achieved. Although this last variant was unsuccessful, we document our attempts to prepare the requisite anhydride. The choice of these anhydrides enables the synthesis of products that will have rigid core structures with several points of diversity derived from the aldehyde, amine, and subsequent functionalization of the carboxylic acid. In addition, further diversification of the nitro group and nitrile is possible for cores 3 and 4. Importantly, the low molecular weight of the core ensures that the final compounds retain, at least to a rough approximation, "drug-like"<sup>24</sup> and "lead-like"<sup>25</sup> molecular properties.

# RESULTS AND DISCUSSION

To more fully exploit the reactivity of substituted succinic anhydrides, we developed a milder and more easily scaled up synthesis of these compounds. Previous syntheses rely on amide bases for enolate generation and were often low yielding for substrates that we required.<sup>23,26</sup> We found that nitrophenylsuccinic

Received:November 8, 2011Revised:January 4, 2012Published:January 6, 2012



Figure 1. Summary of library strategy based on the formal cycloaddition of imines with substituted succinic anhydrides.





anhydrides were the most useful substrates with respect to reactivity and subsequent conversion to more complex substructures.<sup>27</sup> Given that these anhydrides were ultimately derived from the corresponding nitrophenylacetic esters, we reasoned that the requisite alkylation should be possible under mildly basic conditions. Screening a variety of bases and solvents revealed that the combination of  $Cs_2CO_3$  with acetonitrile resulted in the highest yields of alkylation products (eqs 1 and 2; Table 1, entries 2, 7, 10–11).<sup>28</sup> Although the reaction fails for **6c** and gives poor conversion for **6d**, this reaction works well for arylacetic esters with electron-withdrawing groups attached (**6a–b**, **e**), which corresponds to the expected enolate anion stability conferred by delocalization into the ring.

We attempted to apply the mild alkylation conditions for the two additional substrates (Scheme 1). When ethyl cyanoacetate (8) was used as a substrate, dialkylation became the major observable product. Various combinations of NaOEt and NaOt-Bu in

Scheme 1. Alkylation of Cyano- and 2-Benzothiazole Acetic Esters











Scheme 4. Spirocyclization Reactions of 19, 20, and 22



several different solvents invariably resulted in mixtures of unreacted 8 and the mono and dialkylation products 9 and 10. This result is probably due to the highly electron-withdrawing nature of the cyano group paired with the low steric demand when compared to phenyl. Ultimately, the use of NaOEt and ethanol enabled multigram quantities of 9 to be isolated by vacuum distillation. Analogously, mono and dialkylation products 12 and 13, respectively, were competitive when the phenyl ring was replaced by 2-benzothiazole for the alkylation substrate (11). Given the ease with which 9 could be prepared and purified, conversion of this material to the required benzothiazole-substituted succinate ester 12 was more practical.

Succinate esters were cleanly converted to anhydrides in two steps (Scheme 2). Saponification with lithium hydroxide in THF/H<sub>2</sub>O cleaved the diesters to their corresponding diacids. Subsequent dehydration to the anhydrides was best achieved with trifluoroacetic anhydride. Residual TFAA and trifluoroacetic acid were removed by azeotropic removal with toluene, and the resultant anhydrides were generally >90% pure by  ${}^{1}H$ NMR spectroscopy. Although this sequence worked well for the conversion of diesters 7a and 9 to anhydrides 2a and 2b, respectively, attempts to prepare anhydride 2c from benzothiazole 12 were unsuccessful because of degradation of the diacid during the dehydration. Similar results were observed with acetic anhydride and with the neutral dehydration agent 15, which was developed by Kita et al. for the express purpose of preparing heterocycle-fused glutaric anhydrides.<sup>29</sup> There are currently no known heterocycle-substituted succinic anhydrides related to 2c, and we are continuing to examine ways of achieving this difficult dehydration to prepare these potentially useful substrates.

Imine-anhydride reactions of anhydride 2a with imines 16 and 17 proceeded in high yield at room temperature (Scheme 3). Imine 16 is commercially available, whereas 17 was prepared from isobutylamine and benzaldehyde and used without purification. The resultant acids were converted directly to either the corresponding methyl esters 19 or the amides 20-22. Analysis of the diastereoselectivity at the amide stage showed that mixtures varying from 63:37 to 67:33 were generally formed. Although this lack of diastereoselectivity would be a liability for a target-directed synthesis, it is an advantage for diversity-oriented synthesis, provided that the diastereomers are easily separated. At this point isobutyl amides 20a and 20b could be separated into their constituent diastereomers by recrystallization or column chromatography, whereas 21a and 21b exhibited poor solubility and, as a result, were not separable by chromatography. We decided to replace 21 with 22, which had much better solubility, consistent with 20, indicating that the amide NH<sub>2</sub> was problematic. Ester 19b was also easily separated and the major diastereomer formed crystals suitable for X-ray diffraction, confirming the relative configuration of the aromatic rings as 4,5-syn. A similar result was observed for the major diastereomer of amide (20b), and both structures are consistent with previous observations from our laboratory.<sup>23</sup>

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Figure 2. Diversity reagents employed in Scheme 6.

 Table 2. Optimization of Imine Anhydride Reaction Using

 Cyanosuccinic Anhydride



Two strategies for preparing spirooxindoles from imineanhydride products **19**, **20**, and **22** were examined (Scheme 4, Figure 2). Amides **20** and **22** were cyclized under basic conditions. In each case, the spirooxindole products were formed in high yield. Both substrates were reduced to the corresponding anilines using either  $SnCl_2$  and HCl or hydrogen and palladium on carbon. Both sets of conditions produced the anilines in similar yields, and the latter method was generally cleaner and more scaleable. Although there is some precedent for one-step aminolysis and cyclization of methyl esters related to **19**,<sup>30</sup> this transformation proved to be inefficient for our substrates as exemplified by the low yield of **23b** obtained from **19b**.

Cyanosuccinic anhydride 2b reacts with various imines at ambient temperature with high diastereoselectivity (Table 2). Reactions are almost instantaneous and also proceed at reduced temperature. A survey of various solvents revealed conversions were universally high and that reactions in THF proceeded with the highest diastereoselectivity. Using this method, acid 27 was isolated by trituration and filtration in 76% yield as a single detectable diastereomer. The scope of this substrate was explored by using imines formed in situ from amines and aldehydes using triethyl orthoformate as a dehydrating agent (Table 3). The reaction tolerates various substituents on nitrogen (entries 1-6), as well as electron-donating or withdrawing groups on the aldehyde (entries 7 and 8). Isolated yields after conversion to the corresponding methyl esters ranged from 63 to 86%, and in all cases the observed diastereoselectivity was excellent. Reduction of the cyano group of 40 to an aminomethyl group (Scheme 5) followed by acylation with 3,5-dinitrobenzoyl



R <sup>2</sup> 16, 17	$H = \begin{bmatrix} N \\ 23 \\ 2 \\ 2 \\ 23 \\ 23 \\ 23 \\ 23 \\ 23$	$ \begin{array}{c}                                     $
entry	imine <sup><math>a</math></sup> ; R <sup>1</sup> , R <sup>2</sup>	product, yield
1	<b>16</b> <sup><i>b</i></sup> , СН <sub>3</sub> , Н	34, 65%
2	17, <i>i</i> -Bu, H	35, 63%
3	28, <i>i</i> -Pr, H	36, 69%
4	<b>29</b> , CyCH <sub>2</sub> , H	37, 84%
5	<b>30</b> , HC≡CCH <sub>2</sub> , H	38, 60%
6	<b>31</b> , <i>p</i> -ClC <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> , H	<b>39</b> , 86%
7	<b>32</b> , <i>p</i> -ClC <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> , OCH <sub>3</sub>	<b>40</b> , 83%
8	33, <i>p</i> -ClC <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> , CN	41, 65%

<sup>*a*</sup>Imines were formed using 1 equiv of amine, 1 equiv of aldehyde, and 1.6 equiv of HC(OEt)<sub>3</sub> in THF. <sup>*b*</sup>Commercially available imine.

Scheme 5. Reduction and Acylation of 40



chloride produced crystalline amide **42** suitable for analysis by X-ray diffraction. The origin of the high 4,5-anti diastereoselection in this reaction could be thermodynamic or kinetic, and experiments to probe the factors that influence the stereochemical outcome of this reaction are underway.

The amino-spirooxindoles 25 and 26 were employed as synthetic intermediates for diversification by two different reactions (Scheme 6). 25a and 25b were converted to the corresponding azides that underwent smooth cycloaddition reactions with alkynes 43 using sodium ascorbate and copper(II) acetate to form triazoles 44a and 44b. Amines 26a and 26b were Scheme 6. Library Synthesis Using 25, 26, 27, 34





Figure 3. Summary of the molecular properties computed for library members. Calculated partition coefficients (cLogP) are based on the XLOGP method of Wang. $^{31}$ 

converted to amides, ureas, and to sulfonamides using **45**. Cyano-substituted lactam **34** was reduced to the amine using Raney nickel and ammonia, and the resulting amine **49** was also employed in acylation and sulfonylation reactions with **45**. Acid-substituted lactams **27**, produced directly from the imine anhydride reaction, were diversified using a series of amines and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU). The library members were purified by mass-directed fractionation to give 85% or greater of the products in 20–99% yield.

The library produced by the chemistry described above results in a set of compounds with desirable properties for high-throughput screening and the discovery of drug leads and biological probes (Figure 3). The molecular weights range from 200 to 570, which is an ideal range for subsequent modifications by replacing building blocks and/or adding elements of diversity. In addition, the  $cLogP^{31}$  range is favorable, with the vast majority of the compounds falling between one and five. Finally, hydrogen bond donors (0–2) and acceptors (4–9) are both within the accepted ranges for the development of drugs and leads.<sup>24,25</sup>

## CONCLUSION

The synthesis of a "pilot scale" library of complex  $\gamma$ -lactams has been achieved. An optimized protocol for the alkylation of substituted acetate esters allow the large-scale synthesis of succinates under mild conditions. The resulting succinic anhydrides undergo smooth reactions with imines to supply carboxylic acid-appended  $\gamma$ -lactams that can be used in a variety of subsequent diversification reactions. Although we had previously documented the formal cycloaddition reaction for 2fluoro-5-nitrophenylsuccinic anhydride succinic anhydride, this work demonstrates the use of the reaction products in acylation and azide—alkyne cycloaddition (AAC) reactions. Finally, we introduce cyanosuccinic anhydride as a new and highly reactive substrate for the imine-anhydride reaction and show that it also leads to a variety of complex library members.

## ASSOCIATED CONTENT

#### **S** Supporting Information

Detailed experimental procedures, full characterization data, and purification details for all new compounds, as well as .cif files for compounds **19b**, **20b**, and **42**. This material is available free of charge via the Internet at http://pubs.acs.org. In addition, all library members have been submitted to the National Small Molecule Repository where they will be made available for high-throughput screening.

#### AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: jtshaw@ucdavis.edu.

## ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (CAREER award to J.T.S.) and the National Institutes of Health (NCI/R01CA131458; NIGMS/P41GM089153). J.C.F. acknowledges support from the NSF (CHE-0840444) for the purchase of the Bruker SMART DUO diffractometer used for X-ray crystallography. A.L.A. acknowledges research support in the form of a UC Davis President's Undergraduate Fellowship (PUF). C.S. thanks CAPES (Brazilian Coordination for the

Improvement of Higher Education Personnel) for a postdoctoral fellowship. The authors thank Patrick Porubsky (University of Kansas) for conducting mass-directed purification of all final library members at the Center for Methodology and Library Development (KU-CMLD), which is funded by the NIH (NIGMS/P50GM069663). Phillip P. Painter (Tantillo research group, UC Davis) is acknowledged for calculating the molecular properties of the library using OpenEye software (www.eyesopen.com).

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