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Synthesis of a γ -Lactam Library via Formal Cycloaddition of Imines and Substituted Succinic Anhydrides

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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 γ -lactams. 2-Fluoro-5-phenylsuccinic anhydride reacts efficiently with imines to provide lactams that are further diversified by conversion of the nitro group to either an aniline and 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.

Introduction

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

Previous work in our laboratory has employed the formal cycloaddition reaction of imines and anhydrides^{13,21,22} 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.²³ As part of that study, we documented the superior reactivity of phenylsuccinic anhydrides that were substituted with electron-

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Supporting information

Detailed experimental procedures, full characterization data, an 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.

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 SAR, 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. 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”²⁴ and “lead-like”²⁵ molecular properties.

Results and Discussion

In order 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.^{23,26} We found that nitrophenylsuccinic anhydrides were the most useful substrates with respect to reactivity and subsequent conversion to more complex substructures.²⁷ 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 Cs₂CO₃ with acetonitrile resulted in the highest yields of alkylation products (eqs 1 and 2; Table 1, entries 2, 7, 10–11).²⁸ 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 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 multi-gram 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/H₂O 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 ¹H NMR spectroscopy. Although this sequence worked well for the conversion of diesters **7a** and **9** to anhydrides **2a** and **2b**, attempts to prepare anhydride **2c** from benzothiazole **12** were unsuccessful due to 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 for the express purpose of preparing heterocycle-fused glutaric anhydrides.²⁹ 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 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 NH₂ 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.²³

Two strategies for preparing spirooxindoles from imine-anhydride products **19**, **20**, and **22** were examined (Scheme 4). 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 SnCl₂ 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**,³⁰ 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 triethylorthoformate 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 63–86% and in all cases the observed diastereoselectivity was excellent. Reduction of the cyano group of **40** to an aminomethyl group followed by acylation with 3,5-dinitrobenzoyl chloride produced crystalline amide **42** suitable for analysis by X-ray diffraction. The origin of the high 1,2-syn 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. **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 converted to amides, ureas and sulfonamides with **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 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. The molecular weights range from 200 to 570, which is an ideal range for subsequent modifications by replacing building blocks and or adding additional elements of diversity. In addition the cLogP³¹ 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.^{24,25}

Conclusion

The synthesis of a “pilot scale” library of complex γ -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 γ -lactams that can be used in a variety of subsequent diversification reactions. Although we had previously documented the formal cycloaddition reaction for 2-fluoro-5-nitrophenyl 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Mori T, Takahashi K, Kashiwabara M, Uemura D, Katayama C, Iwadare S, Shizuri Y, Mitomo R, Nakano F, Matsuzaki A. Structure of oxazolomycin, a novel β -lactone antibiotic. *Tetrahedron Lett.* 1985; 26:1073–1076.
2. Feling RH, Buchanan GO, Mincer TJ, Kauffman CA, Jensen PR, Fenical W. Salinosporamide a: A highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus salinospora. *Angew Chem, Int Ed.* 2003; 42:355–357.
3. Guntern A, Ioset JR, Queiroz EF, Sandor P, Foggin CM, Hostettmann K. Heliotropamide, a novel oxopyrrolidine-3-carboxamide from heliotropium ovalifolium. *J Nat Prod.* 2003; 66:1550–1553. [PubMed: 14695794]
4. Manam RR, Teisan S, White DJ, Nicholson B, Grodberg J, Neuteboom STC, Lam KS, Mosca DA, Lloyd GK, Potts BCM. Lajollamycin, a nitro-tetraene spiro- β -lactone- γ -lactam antibiotic from the marine actinomycete streptomyces nodosus. *J Nat Prod.* 2005; 68:240–243. [PubMed: 15730252]
5. Okazaki Y, Ishizuka A, Ishihara A, Nishioka T, Iwamura H. New dimeric compounds of avenanthramide phytoalexin in oats. *J Org Chem.* 2007; 72:3830–3839. [PubMed: 17432911]
6. Stuk TL, Assink BK, Bates RC, Erdman DT, Fedij V, Jennings SM, Lassig JA, Smith RJ, Smith TL. An efficient and cost-effective synthesis of pagoclone. *Org Process Res Dev.* 2003; 7:851–855.
7. Masse CE, Morgan AJ, Adams J, Panek JS. Syntheses and biological evaluation of (+)-lactacystin and analogs. *Eur J Org Chem.* 2000:2513–2528.
8. Fenical W, Jensen PR, Palladino MA, Lam KS, Lloyd GK, Potts BC. Discovery and development of the anticancer agent salinosporamide a (npi-0052). *Bioorg Med Chem.* 2009; 17:2175–2180. [PubMed: 19022674]
9. Ng PY, Tang Y, Knosp WM, Stadler HS, Shaw JT. Synthesis of diverse lactam carboxamides leading to the discovery of a new transcription-factor inhibitor. *Angew Chem, Int Ed.* 2007; 46:5352–5355.
10. Marti C, Carreira EM. Construction of spiro[pyrrolidine-3,3'-oxindoles] - recent applications to the synthesis of oxindole alkaloids. *Eur J Org Chem.* 2003:2209–2219.
11. Edmondson S, Danishefsky SJ, Sepp-Lorenzino L, Rosen N. Total synthesis of spirotryprostatin a, leading to the discovery of some biologically promising analogs. *J Am Chem Soc.* 1999; 121:2147–2155.
12. Cravotto G, Giovenzana GB, Pilati T, Sisti M, Palmisano G. Azomethine ylide cycloaddition/reductive heterocyclization approach to oxindole alkaloids: Asymmetric synthesis of (–)-horsfiline. *J Org Chem.* 2001; 66:8447–8453. [PubMed: 11735524]
13. Ng PY, Masse CE, Shaw JT. Cycloaddition reactions of imines with 3-thiosuccinic anhydrides: Synthesis of the tricyclic core of martinellie acid. *Org Lett.* 2006; 8:3999–4002. [PubMed: 16928058]
14. Wei JQ, Shaw JT. Diastereoselective synthesis of γ -lactams by a one-pot, four-component reaction. *Org Lett.* 2007; 9:4077–4080. [PubMed: 17760458]
15. Tan DQ, Martin KS, Fetting JC, Shaw JT. Ammonia synthons for the multicomponent assembly of complex γ -lactams. *Proc Natl Acad Sci US A.* 2011; 108:6781–6786.
16. Lettan RB, Galliford CV, Woodward CC, Scheidt KA. Amide enolate additions to acylsilanes: In situ generation of unusual and stereoselective homoenolate equivalents. *J Am Chem Soc.* 2009; 131:8805–8814. [PubMed: 19505076]
17. Raup DEA, Cardinal-David B, Holte D, Scheidt KA. Cooperative catalysis by carbenes and Lewis acids in a highly stereoselective route to γ -lactams. *Nat Chem.* 2010; 2:766–771. [PubMed: 20729898]
18. Zhao X, DiRocco DA, Rovis T. N-heterocyclic carbene and Brønsted acid cooperative catalysis: Asymmetric synthesis of trans- γ -lactams. *J Am Chem Soc.* 2011; 133:12466–12469. [PubMed: 21780842]
19. Galliford CV, Scheidt KA. Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. *Angew Chem, Int Ed.* 2007; 46:8748–8758.
20. Marti C, Carreira Erick M. Construction of spiro[pyrrolidine-3, 3'-oxindoles] – recent applications to the synthesis of oxindole alkaloids. *Eur J Org Chem.* 2003; 2003:2209–2219.

21. Cushman M, Madaj EJ. A study and mechanistic interpretation of the electronic and steric effects that determine the stereochemical outcome of the reaction of schiff bases with homophthalic anhydride and 3-phenylsuccinic anhydride. *J Org Chem.* 1987; 52:907–915.
22. Gonzalez-Lopez M, Shaw JT. Cyclic anhydrides in formal cycloadditions and multicomponent reactions. *Chem Rev.* 2009; 109:164–189. [PubMed: 19140773]
23. Masse CE, Ng PY, Fukase Y, Sanchez-Rosello M, Shaw JT. Divergent structural complexity from a linear reaction sequence: Synthesis of fused and spirobicyclic γ -lactams from common synthetic precursors. *J Comb Chem.* 2006; 8:293–296. [PubMed: 16676997]
24. Lipinski CA. Lead- and drug-like compounds: The rule-of-five revolution. *Drug Discovery Today: Technologies.* 2004; 1:337–341.
25. Hann MM, Oprea TI. Pursuing the leadlikeness concept in pharmaceutical research. *Curr Opin Chem Biol.* 2004; 8:255–263. [PubMed: 15183323]
26. Casimir JR, Ettouati L, Paris J. An efficient synthesis of anhydrides of 2-monosubstituted succinic acid monoesters and their application to the dakin-west reaction: Isolation of some 5-succinyloxyoxazole intermediates. *Lett Pept Sci.* 1998; 5:13–18.
27. Masse CE, Ng PY, Fukase Y, Sanchez-Rosello M, Shaw JT. Divergent structural complexity from a linear reaction sequence: Synthesis of fused and spirobicyclic γ -lactams from common synthetic precursors. *J Comb Chem.* 2006; 8:293–296. [PubMed: 16676997]
28. Kim JM, Kim SH, Lee HS, Kim JN. An expedient aralkylation of Baylis-Hillman adduct via the pd-catalyzed decarboxylative protonation strategy. *Tetrahedron Lett.* 2009; 50:1734–1737.
29. Kita Y, Akai S, Ajimura N, Yoshigi M, Tsugoshi T, Yasuda H, Tamura Y. Facile and efficient syntheses of carboxylic anhydrides and amides using (trimethylsilyl)ethoxyacetylene. *J Org Chem.* 1986; 51:4150–4158.
30. Luehr, GW.; Jain, R.; Renslo, A.; Josyula, VPVN.; Gordeev, MF. Preparation of oxazolidinones containing oxindoles as antibacterial agents. 20050728. 2006. 2005–191752 20060030609
31. Wang R, Fu Y, Lai L. A new atom-additive method for calculating partition coefficients. *J Chem Inf Comput Sci.* 1997; 37:615–621.

Figure 1.
Summary of Library Strategy Based on the Formal Cycloaddition of Imines with Substituted Succinic Anhydrides.

Figure 2.
Diversity Reagents Employed in Scheme 4.

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

$\text{Cs}_2\text{CO}_3/\text{CH}_3\text{CN}$; 80 °C

9:10 = <5:>95

NaOEt/EtOH ; 0 to 23 °C

9:10 = 59:41; 20% yield of 9

$\text{Cs}_2\text{CO}_3/\text{CH}_3\text{CN}$; 80 °C

12:13 = <5:>95, 64%

NaOEt/EtOH ; 0 to 23 °C

12:13 = 19:81

Scheme 1.

Alkylation of Cyano- and 2-Benzothiazole Acetic Esters.

Scheme 2.

Conversion of Diesters to Substituted Succinic Anhydrides.

Scheme 3.
 Imine-Anhydride Reactions of **2a** Followed by Ester and Amide Formation.

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

Scheme 5.
Reduction and Acylation of **40**.

Scheme 6.
Library Synthesis Using **25**, **26**, **27**, **34**.

Table 1

Optimization of the Alkylation of Substituted Phenylacetic Acid Esters

(1)

(2)

Entry	Substrate	Solvent/Base	Temp.	Yield
1	6a	CH ₃ CN/Cs ₂ CO ₃	23 °C	13%
2	6a	CH ₃ CN/Cs ₂ CO ₃	80 °C	87%
3	6a	DMF/Cs ₂ CO ₃	23 °C	38%
4	6a	DMF/Cs ₂ CO ₃	100 °C	49%
5	6a	THF/Cs ₂ CO ₃	23 °C	14%
6	6a	THF/Cs ₂ CO ₃	reflux	33%
7	6b	CH ₃ CN/Cs ₂ CO ₃	23 °C	77%
8	6c	CH ₃ CN/Cs ₂ CO ₃	80 °C	--
9	6d	CH ₃ CN/Cs ₂ CO ₃	23 °C	8%
10	6d	CH ₃ CN/Cs ₂ CO ₃	80 °C	34%
11	6e	CH ₃ CN/Cs ₂ CO ₃	80 °C	71%

Table 2

Optimization of Imine Anhydride Reaction Using Cyanosuccinic Anhydride.

entry	solvent	dr	conversion (isolated yield)
1	CHCl ₃	79:21	96%
2	ACN	78:22	93%
3	DCM	75:25	>98%
4	THF	93:7	>98% (76%)
5	DMF	66:34	96%
6	PhMe	63:37	>98%

Table 3Imine Anhydride Reactions of Cyanosuccinic Anhydride **2b**.

entry	imine ^a ; R ¹ , R ²	Product, Yield
1	16 ^b , CH ₃ , H	34 , 65%
2	17 , <i>i</i> -Bu, H	35 , 63%
3	28 , <i>i</i> -Pr, H	36 , 69%
4	29 , CyCH ₂ , H	37 , 84%
5	30 , HC≡CCH ₂ , H	38 , 60%
6	31 , <i>p</i> -ClC ₆ H ₄ CH ₂ , H	39 , 86%
7	32 , <i>p</i> -ClC ₆ H ₄ CH ₂ , OCH ₃	40 , 83%
8	33 , <i>p</i> -ClC ₆ H ₄ CH ₂ , CN	41 , 65%

^a Imines were formed using 1 equiv. amine, 1 equiv. aldehyde, and 1.6 equiv. HC(OEt)₃ in THF.^b Commercially available imine.