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Architecturally diverse heterocycle formation by *N*-acyliminium ion initiated cyclization

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Dedicated to Professor Larry Overman on occasion of his 60th birthday

Abstract—Enaminoesters containing a tethered indole or aryl moiety on the amine react with substituted maleic anhydrides or acryloyl chlorides to provide pyrrolinone or dihydropyridone products, respectively. The indole-tethered dihydropyridones can be induced to undergo a one-pot cyclization whereas, the indole-tethered pyrrolinone intermediates are readily cyclized with HCl. The aryl-tethered pyrrolinones or dihydropyridones can be isolated and subsequently induced to cyclize with triflic acid. This methodology culminates in the synthesis of erythrane-like and other natural products that are readily amenable to combinatorial library production.

The desire for structurally diverse, natural product-like scaffolds to populate large sets of structurally complex molecules prompted us to explore various cyclization reactions which afford the desired degree of product complexity and functional diversity.[1] The *N*-acyliminium ion cyclization protocol to prepare alkaloid natural products has been utilized with great effect over the past 30 years to this end.[2] Recently, Padwa[3a,b] developed a general procedure for heterocycle synthesis by using a Pummerer induced thionium ion to initiate the intermediacy of an *N*-acyliminium ion for subsequent olefin or aryl termination. Katzenellenbogen[3c] and Kirkpatrick[3d] also utilized *N*-acyliminium ions in the synthesis of diverse hexahydrobenzoisoquinolines.

Using an *N*-acyliminium ion as a key intermediate in a multistep cyclization sequence, we have developed a simple two or three-step procedure to natural product-like heterocyclic scaffolds and templates. At the outset we prepared β-enamino ethyl esters of tryptamine, homovalerylamine, 2,5-dimethoxyphenethylamine, phenethylamine and 2-thienylphenethylamine as the principal starting materials by condensation with ethyl acetoacetate.

The combination of the β-enamino ester with an acryloyl chloride results in an aza-annulation[4] forming a pyridone with a new cyclic β-enamino ester (Fig. 1; Table 1).

At this stage, the indolylethylpyridones prepared from any of the three acryloyl chlorides (methallyl, crotonyl and acryloyl) proceed onward (50–60°C, 3 h) to tetracycle formation via the intermediacy of an *N*-acyliminium ion catalyzed by the HCl released from the reaction, (Fig. 2; example **1**, Table 1). The use of methallyl and crotonyl chloride provides substituted pyridones with an α or β methyl, respectively. These substituents induced complete 1,3 and 1,2-relative asymmetric induction, respectively, on the resulting dihydropyridone ring during the final cyclization, presumably due to a preference for pseudo-equatorial alignment of the substituents prior to protonation and

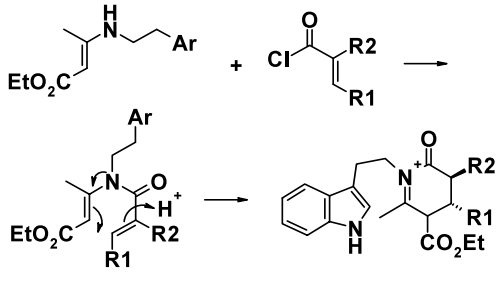

Figure 1. Proposed stepwise mechanism with indole tethered pyridones.

Keywords: indoles; *N*-acyliminium ion; erythrane; tryptamine; Pictet–Spengler.

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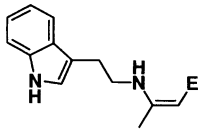
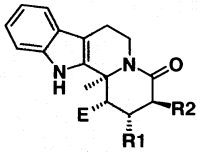
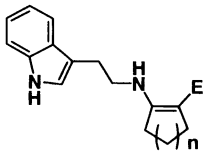
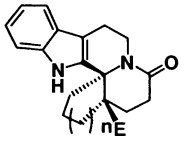
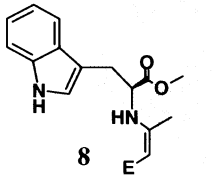
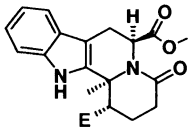
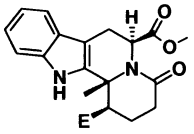
Table 1. Tryptamine β-enamino ethyl esters as precursors for *N*-acyliminium ion cyclizations[a]

Starting β-Enamino Ester E = CO_2Et	Products		Yield (%)[b,c]
 **1**	THF, 50 °C, 1-2 h, 1.3 equiv. acryloyl, crotonyl, or methallyl chloride →  **2-4**	**2** R1=R2=H **3** R1=CH_3, R2=H **4** R1=H, R2=CH_3	79 50 40
 **5** n = 1, 2	THF, 65 °C, 2 h, 1.3 equiv. acryloyl chloride →  **6-7**	**6** n = 1 **7** n = 2	86 78
 **8**	THF, 50 °C, 2 h acryloyl chloride →  **9** +  **10**	**9:10** 1:1 ratio	45

a) Compounds **5**, n = 1,2, were prepared by condensation with 2-ethoxycarbonyl-1-cyclopentanone (97%) and 2-ethoxycarbonyl-1-cyclohexanone (94%) in $CHCl_3$. CSA = camphorsulphonic acid.

b) All yields refer to isolated, racemic compounds that were fully characterized by ^1H NMR(400 MHz), ^{13}C NMR (100 MHz), DEPT, 2D ^1H COSY, 2D NOESY, IR and LCMS.

c) Example **8** used chiral L-Tryptophan methyl ester.

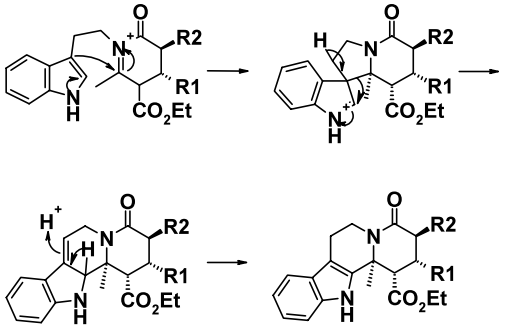


Figure 2. *N*-Acyliminium ion induced cyclization.

formation of the *N*-acyliminium ion. The protonation will ultimately take place from the least hindered face of the enamino ester providing an axial ester, so as to minimize interaction with the iminium methyl substituent (the relative configuration was determined through analysis of the 2-D ^1H COSY and 2-D NOESY experiments at 400 MHz).

The original β-enamino ester substrates can, on the other hand, be combined with maleic, citraconic or itaconic anhydride to form a pyrrolinone or dihydropyridone bearing an acetic acid residue, (Fig. 3; examples **11** and **13**, Table 2).

These structures, likewise, undergo the *N*-acyliminium ion induced cyclizations. The foregoing reactions demonstrate the one-pot formation of three stereospecific centers along the newly formed piperidinone or pyrrolidinone backbone of the final tetracycle. Enamino ester **8**, when subjected to acryloyl chloride, provided two tetracycles, **9** and **10**, in a 1:1 ratio.

The lack of stereoselectivity in the ring formation implies that an asymmetric center external to the dihydropyridone ring does not induce any facial selectivity during the protonation giving the *N*-acyliminium ion intermediate. The pyrrolinones and dihydropyridones with α-acetic acid side chains and tethered indoles require the addition of dry HCl (~1.5 equiv. from 4 M HCl in dioxane, 70°C, 3 h) to accomplish ring closure of the initial anhydride–enamine adduct since there is no liberated HCl present as is the case with the acryloyl chloride additions.

Dihydropyridones or pyrrolinones with methoxy substituted aryl rings require the aid of triflic acid (TfOH, 1 equiv.) in 1,2-dichloroethane or dioxane (~50°C, 1 h) to effect ring closure (Table 3).

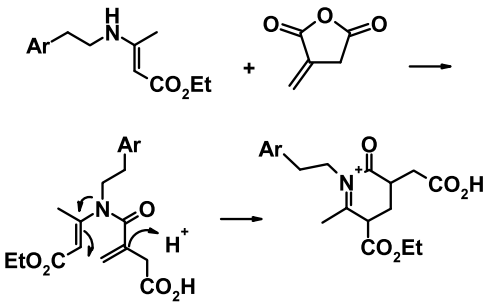


Figure 3. Anhydride addition to β-enamine.

It is not clear why compounds with tethered phenyl groups require a stronger protonator like triflic acid to initiate the formation of the *N*-acyliminium ion as opposed to the indole series, which favors the use of HCl to the same end. Quinolizinones **18**[5] and **21** demonstrate that two and three contiguous asymmetric centers, respectively, can be prepared quickly, analogous to the indolo substrates **2** and **3** of Table 1. Example **24** shows that only the *syn* ring juncture is obtained upon cyclization in accord with previous work.[6] Enaminoester **25** can be utilized in the formation of an erythrinane-like class of alkaloids. Reaction of the β-enaminoester with maleic anhydride results in the stereospecific formation[7] of indolizine **26** with the acetic acid side chain *cis* to the tertiary carboethoxy-group in excellent yield. Final cyclization to the erythrane skeleton does not epimerize the α center next to the amide carbonyl.

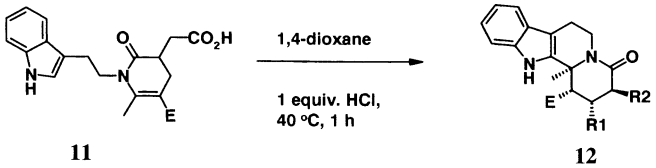
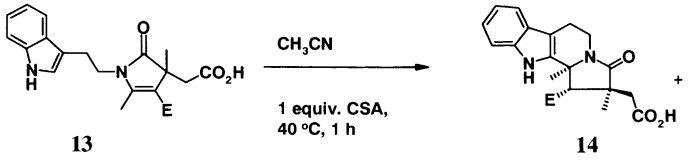
Enaminoester **28** undergoes clean aza-annulation to the dihydropyridone using acryloyl chloride (easily followed by thin-layer chromatography). After 1 h at room temperature, an equivalent of triflic acid is added and the mixture warmed to 45°C for 1 h. This provides **30** in 65% yield as a 4:1 (α/β) mixture. Similar conditions for enaminoester **31** gave compound **33** as 3:1 (α/β) mixture. These examples show that a basic one-pot sequence can be utilized in the preparation of these heterocycles if one uses the acryloyl chloride aza-annulation with an aryl tether.

In summation, we have developed a unique and general *N*-acyliminium ion methodology to prepare natural product-like substrates for diverse combinatorial libraries. We are continuing to explore this protocol by looking at other ring systems and ring sizes, by using more elaborate β-ketoesters to prepare the β-enaminoesters and exploring Lewis acids by which to conduct these cyclizations enantiospecifically.

Acknowledgements

We would like to thank Betty Fitzgerald for her expertise in obtaining COSY, NOESY, IR and LCMS spectra. We would also like to thank Richard Gless and Paul Baures for critical and insightful commentary on this manuscript.

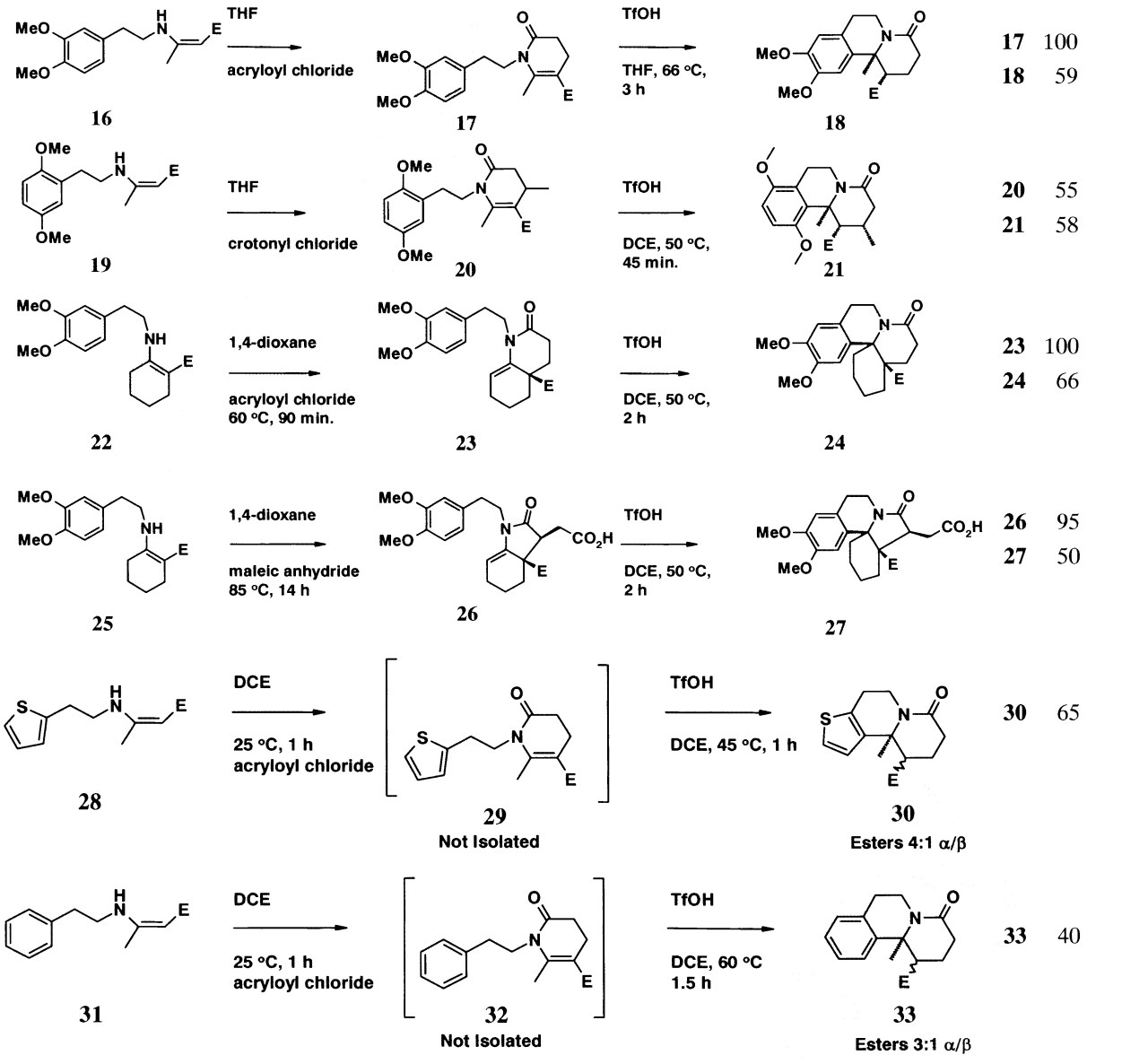
Table 2. Cyclic anhydrides as the acylation component[a]

Starting β-Enamino Ester E = CO_2Et	Products	Yield (%)[b]
 11	1,4-dioxane; 1 equiv. HCl, 40 °C, 1 h → 12	**12** R1=H, R2=CH_2CO_2H	100
 13	CH_3CN; 1 equiv. CSA, 40 °C, 1 h → 14 + 15	**14:15** 1.9:1 ratio	47

a) Compounds **11** (80%) and **13** (70%) were prepared by reaction of itaconic and citraconic anhydride with compound **1** respectively, in refluxing 1,4-dioxane. CSA = camphorsulphonic acid.

b) All yields refer to isolated, racemic compounds that were fully characterized by ^1H NMR(400 MHz), ^{13}C NMR (100 MHz), DEPT, 2D ^1H COSY, 2D NOESY, IR and LCMS.

Table 3. β-Aryl phenethyl amino-enamino ethyl esters as precursors for *N*-acyliminium ion cyclization[a]



a) Terms: DCE = 1,2-dichloroethane; TfOH = Triflic Acid.

b) All yields refer to isolated, racemic compounds that were fully characterized by ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), DEPT, 2D ^{1}H COSY, 2D NOESY, IR and LCMS.

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