Graphical Abstract

Utility and NMR Studies of Unsaturated Acylammonium Salts: Synthesis of Polycyclic Dihydropyranones and Dihydropyridone

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Utility and NMR studies of α,β -unsaturated acylammonium salts: Synthesis of polycyclic dihydropyranones and a dihydropyridone

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ABSTRACT

Organocatalyzed, tandem Michael-lactonizations and a lactamization employing cyclic 1,3-dicarbonyl and an enamino ketone, respectively, were achieved through the intermediacy of α,β -unsaturated acylammonium salts derived from commodity acid chlorides or *in situ* generated enol esters. 4-Dimethylaminopyridine (DMAP) promotes this process providing the corresponding polycyclic dihydropyranones and a dihydropyridone in good yields. The utility of this methodology was demonstrated in the formal synthesis of the alkaloid dielsine and the anticoagulant warfarin. Comparative ^{13}C NMR studies of acylammonium salt intermediates provide insights into the impact of their formation on the reactivity of the β -carbon.

Keywords:

Organocatalysis
4-dimethylaminopyridine (DMAP)
Coumarin
Warfarin
Dielsine
NMR study

Dihydropyranones (enol lactones) are frequently encountered structural sub-units in natural products and bioactive compounds. For instance, these heterocycles constitute the basic skeleton of the neoflavonoid, coumarin and iridoide family of natural products.¹ They are also versatile intermediates for the synthesis of 2-pyranones, γ -lactones, cyclic enamines, and substituted benzenoids.² Arguably, the reaction of α,β -unsaturated acid derivatives with cyclic 1,3-dicarbonyls is the most direct method for the synthesis of enol lactones, but established methods based on this process suffer from harsh reaction conditions (*e.g.* pyridine, reflux).³ An important advance in this area occurred when Kanemasa and Itoh discovered an asymmetric Michael reaction between a 1,3-diketone and α,β -unsaturated acylpyrazole, catalyzed by a chiral Lewis acid/achiral amine combination.⁴ This process afforded enol lactones with excellent enantioselectivity but required the synthesis of acylpyrazole as Michael acceptors. The renewed interest in catalytic enol lactone synthesis can be attributed to the concept of “conjugated acylazoliums,” introduced independently by Lupton,⁵ Bode⁶ and Studer.⁷ These *N*-heterocyclic carbene (NHC) catalyzed reactions require either a stoichiometric amount of oxidant or functionalized aldehydes or esters as starting materials and have focused primarily on acyclic 1,3-dicarbonyl compounds.⁸ These limitations, coupled to our recent studies of chiral α,β -unsaturated acylammonium salts enabling Michael-aldol- β -lactonization,⁹ Michael-proton transfer-lactamization,¹⁰ and Diels-Alder-lactonization¹¹ organocascades, prompted us to reinvestigate the original idea of making cyclic enol lactones from unsaturated acid derivatives through organocatalysis with achiral and chiral Lewis bases under mild conditions.¹² In particular, the use of mono- and bicyclic 1,3-dicarbonyls in these reactions have not been described and thus we focused on these substrates. Herein, we report a mild, direct synthesis of polycyclic dihydropyranones and a dihydropyridone from acid chlorides *via* α,β -unsaturated acylammonium salts and cyclic 1,3-dicarbonyl compounds,

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promoted by 4-dimethylaminopyridine (DMAP). Furthermore, we have found that an enantioselective version of this reaction is also feasible by using a chiral Lewis base.

Previous work by Smith et al.

Previous work by Romo et al.

This work

Scheme 1. Enol lactone synthesis employing α,β -unsaturated, acylammonium salt catalysis. HBTM 2.1 = homobenzotetramisole 2.1, TMSQN = *O*-trimethylsilylquinine.

In the area of asymmetric organocatalysis, chiral α,β -unsaturated acylammonium salts are beginning to draw greater attention.¹³ A remarkable innovation in this area occurred when Fu and co-workers discovered a [3 + 2] annulation of an indene with a chiral α,β -unsaturated acylammonium salt derived from α,β -unsaturated acid fluorides to produce diquinanes, catalyzed by a chiral PPY derivative.¹⁴ This work provided a logical framework for catalytic generation and the use of chiral α,β -unsaturated acylammonium salts. Very recently, the Smith group¹⁵ and our group¹⁰ have independently disclosed the use of these intermediates in Michael-lactonization and Michael-lactamization organocascades (Scheme 1) in combination with simple, acyclic 1,3-dicarbonyl compounds. Furthermore, we also demonstrated the full potential of α,β -unsaturated acylammonium salts in enabling formation of three new bonds through Michael-aldol-lactonization⁹ and Diels-Alder-lactonization organocascades.¹¹ Building on these studies, we sought to explore the use of cyclic 1,3-dicarbonyls and enamino ketones to access polycyclic dihydropyranones and dihydropyridinones using unsaturated acylammonium salts.

During our previous studies of the asymmetric Michael enol-lactonization,¹⁰ we briefly explored the cyclic 1,3-dicarbonyl, 1,3-cyclohexanedione (**2a**), as Michael donor with *O*-trimethylsilylquinine (TMSQN) as catalyst. However, one of the reaction conditions that worked well for acyclic 1,3-dicarbonyl compounds, gave a mixture of the desired enol lactone **3a** (33%, 96% ee) and the enol ester **4** (29%) (Scheme 2). Thus, we sought to identify conditions to exclusively generate polycyclic dihydropyranones.

Scheme 2. Attempted asymmetric, Michael-enol lactonization with 1,3-cyclohexanedione (**2a**)

We initiated our studies in the absence of catalyst and base, and as expected no product was observed (Table 1, entry 1). Addition of only Hünig's base gave predominantly enol ester **4a** (60%), whereas the stronger Brønsted base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), gave a mixture of products in which the enol lactone **3a** was the minor product

(entries 2, 3). The use of catalytic DBU led to inferior results (entry 4). After initial screening of Brønsted bases, we focused upon a suitable Lewis base to generate α,β -unsaturated acylammonium from **1a**, however it should be noted that DBU has previously been shown to also serve as a Lewis base.¹⁶ Use of a catalytic amount of DMAP, led to exclusive formation of the desired enol lactone **3a** in 92% yield (entry 5) and use of 4-(1-pyrrolidiny)pyridine (4-PPY) gave comparable results (entry 6). Lewis acid additives, such as LiClO₄, did not provide further improvements in yield (entry 7) nor did raising the temperature to 50 °C (entry 8). These results suggested the possibility that the initially formed enol ester **4a** could be converted to the desired enol lactone **3a** through regeneration of an acylammonium intermediate. Thus, we subjected the isolated enol ester **4a** to the optimal conditions devoid of DMAP and indeed obtained lactone **3a**. However, optimal results for conversion (68%) were only obtained when an additional 1.0 equiv of cyclohexanedione (**2a**) was added.

Table 1. Screening of catalysts and reaction conditions for the racemic Michael-enol lactonizations of **2a**

entry ^a	Brønsted base	Lewis base	% yield (3a) ^b	% yield (4a) ^b
1	-	-	-	-
2	DIPEA	-	>5	60
3	DBU	-	24	56
4	DIPEA	DBU	10	80
5	DBU	DMAP	92	-
6	DBU	4-PPY	84	-
7	DBU+LiClO ₄	DMAP	86	-
8 ^c	DBU	DMAP	82	>5

[a] The reactions were performed with 2.0 mmol **1a** and 4.0 mmol of **2a**, (0.1 M solution), [b] Yield of isolated product. [c] Reaction was conducted at 50 °C for 24 h.

With optimized conditions in hand, a variety of cyclic 1,3-dicarbonyls **2a-f** were studied along with several commodity acid chlorides **1a-e** bearing both aliphatic and aromatic β -substituents leading to dihydropyranones **3a-k** (Table 2). Both β -methyl and β -phenyl acryloyl chlorides led to dihydropyranones (entry 1). However, α,β -disubstituted acid chlorides did not participate (not shown). Substitution on the 1,3-cyclohexanedione was also tested and the results were fairly invariant. For instance, 5,5-dimethyl and 5-phenyl derivatives afforded the corresponding dihydropyranones, with the latter delivering a 1:1 diastereomeric mixture as expected (entries 2, 3). These results prompted us to extend this reaction to 4-hydroxycoumarin **2d**, with a view to synthesize dihydropyranocoumarins, which are known to possess various biological activities including anticoagulant activity.¹⁷ The reaction worked well with β -methyl, β -phenyl, α -methyl and β -4-chlorophenyl acryloyl chlorides **1a-d** delivering enol lactones **3e – 3h**, but did not afford the desired product with an electron rich aromatic (*e.g.* β -4-methoxyphenyl acryloyl chloride **1e**). 4-Hydroxy-6-methyl-2-pyrone (**2e**) and 4-hydroxy-1-methyl-1,2-dihydroquinolin-2-one (**2f**) also participated in the Michael enol-lactonization with comparable efficiency (entries 5, 6).

Table 2. Michael enol-lactonization with cyclic 1,3-dicarbonyls **2a-f** and commodity acid chlorides **1a-e**

$ \begin{array}{c} \text{R}^1 \text{---} \text{CH}=\text{CH} \text{---} \text{C}(=\text{O})\text{Cl} \\ \text{R}^2 \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{O} \\ \parallel \quad \parallel \\ \text{O} \quad \text{O} \end{array} \xrightarrow[\text{DBU, CH}_2\text{Cl}_2, 23^\circ\text{C, 72 h}]{\text{DMAP (20 mol\%)}} \begin{array}{c} \text{O} \\ \parallel \\ \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{O} \\ \parallel \quad \parallel \\ \text{O} \quad \text{O} \end{array} $				
	1a R ¹ =Me, R ² =H 1b R ¹ =Ph, R ² =H 1c R ¹ =H, R ² =Me 1d R ¹ =4-ClC ₆ H ₄ , R ² =H 1e R ¹ =4-(MeO)C ₆ H ₄ , R ² =H	2a-f	3a-k	
entry ^a	acid chloride	dicarbonyl	enol-lactone	% yield ^b
1	1a	2a	3a R ¹ =Me, R ² =H	92
	1b		3b R ¹ =Ph, R ² =H	65
2	1a	2b	3c	87
			3d	
3	1a	2c	3d	84 (dr 1:1)
4	1a	2d	3e R ¹ =Me, R ² =H	87
	1b		3f R ¹ =Ph, R ² =H	70
	1c		3g R ¹ =H, R ² =Me	61
	1d		3h R ¹ =4-ClC ₆ H ₄ , R ² =H	52
	1e		3i R ¹ =4-(MeO)C ₆ H ₄ , R ² =H	0
5	1a	2e	3j	86
6 ^c	1a	2f	3k	72

[a] The reactions were performed with 2.0 mmol acid chlorides **1a-e** and 4.0 mmol of dicarbonyl **2a-f** (0.1 M solution). [b] Yield of isolated product. [c] Reaction was conducted at 50 °C.

The synthetic utility of the described annulation was demonstrated through the use of adduct **3f** to access the well-known anticoagulant warfarin **5**.¹⁸ The conversion was carried out by adding MeLi to an *in situ* generated Weinreb amide derived from **3f**.

Scheme 3. Synthesis of the anticoagulant warfarin (**5**) from enol lactone **3f**

The described annulation was also applied to a formal synthesis of the azafluorenone alkaloid, dielsine. The Michael enol-lactamization of crotonyl chloride (**1a**) with enamine **6**

afforded dihydropyridone **7**, which was previously converted to dielsine (**8**) in two steps.¹⁹ Dihydropyridones, such as **7**, were previously employed in the syntheses of various drug candidates and this core structure is found in many natural products.²⁰

Scheme 4. Formal synthesis of dielsine (**8**)

A proposed pathway for the annulation process for crotonyl chloride (**1a**) and 1,3-cyclohexanedione (**2a**) is shown in Scheme 5. Following its formation with DBU, the enolate **II** undergoes conjugate addition to the acylammonium salt **I**, derived from **1a** and DMAP, proton transfer to generate enolate **IV** and finally intramolecular enol-lactonization to regenerate DMAP. A crossover experiment between enol ester **4a** and cinnamoyl chloride (**1b**) under optimized reaction conditions indeed gave crossover products **3b** and **10** in 12% and 15% respectively, which further supports reversible enol ester formation (Scheme 5b). This crossover experiment also indicates that an alternative pathway, involving a Claisen [3,3] rearrangement of tetrahedral intermediate **V**, as previously described by Bode⁶ for a related transformation employing NHC catalysts, cannot be the exclusive pathway for product formation.

Scheme 5. Postulated pathway for the Michael enol-lactonization as shown for crotonyl chloride (**1a**) and 1,3-cyclohexanedione (**2a**); b) Crossover experiment with enol ester **4a** and cinnamoyl chloride (**1b**).

To gain insight into the degree of activation of acid chlorides upon formation of derived α,β -unsaturated acylammonium salts,⁸⁻¹⁰ revealed during our previous studies of various organocascade processes, the ¹³C NMR chemical shift of the β -carbon (C3) was

determined for various acylammonium salts. In analogy to a method previously used to measure the Lewis acidity of various Lewis acids upon complexation to α,β -unsaturated carbonyl compounds,²¹ we measured the chemical shift differences of the β -carbon upon reaction of crotonyl chloride **1a** with several Lewis bases in comparison to the starting acid chloride and a related tertiary amide **9a**. However, Lewis acid activation presumably occurs through inductive π -system activation upon Lewis acid complexation to the carbonyl oxygen lone pair leading to reduced electron density at the β -carbon and a greater downfield chemical shift for stronger Lewis acids. In the case of acylammonium salt formation from acid chlorides, activation, if any, would presumably result from inductive effects propagated through the σ -framework, which may also be revealed through reduced electron density at the β -carbon. We therefore measured the ^{13}C chemical shifts in CDCl_3 at 23 °C for various acylammonium salts formed through reaction of an acid chloride with various tertiary amines (Table 3).

The ^{13}C chemical shifts of crotonyl chloride (δ 152.9) and the derived morpholino amide **9a** (δ 142.0) were measured and used as comparators (Table 3, entries 1 and 2). As expected, the acid chloride has a significant downfield chemical shift for the β -carbon ($\Delta\delta$ -10.9) compared to the amide. The use of the tertiary amine, *N*-methyl morpholine, led to acylammonium salt **9b** with a significant downfield chemical shift for the β -carbon ($\Delta\delta$ -7.6) compared to amide **9a** but not to the extent of crotonyl chloride ($\Delta\delta$ -10.9). The use of pyridine led to acylpyridinium salt **9c** that had a nearly identical chemical shift for the β -carbon (entry 4) as the *N*-methyl morpholine derived salt **9b**. It should be noted that in the case of *N*-methylmorpholine and pyridine, unreacted Lewis base and acid chloride remained suggestive of an equilibrium between the acid chlorides and the derived acylpyridinium salts.²² On the other hand, the use of DMAP and 9-azajulolidine led to complete conversion and significant downfield shifts of the β -carbon compared to the acid chloride ($\Delta\delta$ -3.9, -2.7 respectively) suggestive of decreased reversibility and the deshielding effect of the positive charge in these intermediates, respectively. The observed chemical shifts could also suggest that the ability to delocalize the positive charge on nitrogen to a greater extent through substituted pyridinium intermediates may lead to lower electron density at the β -carbon and this is borne out by consideration of contributing resonance structures (Scheme 6). In the case of the chiral Lewis base benzotetramisole (BTM), a significant change in the chemical shift of the β -carbon compared to the acid chloride was not observed (entry 7). However, it is also important to note that formation of isothioureas-based acylammonium salts is expected to lead to steric impediment at the carbonyl carbon, which slows 1,2-addition enabling 1,4-addition to become the predominant pathway. Thus, formation of chiral acylammonium salts with isothioureas and cinchona alkaloids may not lead to dramatic activation of the β -carbon but rather a significant decrease in 1,2-reactivity enabling these Michael-initiated organocascades. Of the acylammonium salts studied, two groups of these intermediates appear to emerge. One group possesses a more localized positive charge on nitrogen and are formed reversibly²² (highlighted in blue) while a second group possesses a delocalized positive charge and are formed irreversibly (highlighted in red) reflected in the observed chemical shift differences of the β -carbons.

Table 3. ^{13}C NMR analysis of various acylammonium salts and comparison to an acid chloride and amide.

$ \begin{array}{ccc} \begin{array}{c} \text{O} \\ \parallel \\ \text{Cl}-\text{C}-\text{CH}=\text{Me} \\ \text{1} \quad \text{2} \quad \text{3} \\ \text{1a} \end{array} & \xrightarrow[\substack{\text{CDCl}_3 \\ 30 \text{ min} - 18 \text{ h} \\ (0.2 \text{ M})}]{\text{Lewis base}} & \begin{array}{c} \text{O} \quad \text{H} \\ \parallel \quad \text{3} \\ \text{R}-\text{C}=\text{CH}-\text{Me} \\ \text{1} \quad \text{2} \\ \text{9a-f} \end{array} \end{array} $				
entry	Lewis base	R	^{13}C NMR δ (ppm)	
			C3	$\Delta\delta$ C3 ^a
1	-	Cl	152.9	-
2	morpholine	9a	142.0	+10.9
3	<i>N</i> -methyl morpholine ^b	9b	149.6	+3.3
4	pyridine ^b	9c	149.6	+3.3
5	DMAP	9d	156.8	-3.9
6	9-azajulolidine	9e	155.6	-2.7
7	(+)-BTM	9f	152.4	-0.5

^aChange in chemical shift for ^{13}C of C3 in the acylammonium salt relative to C3 of acid chloride; ^bIn these cases, complete conversion to the corresponding acylammonium salts was never observed as judged by NMR. DHIB = 2,3-dihydro-2*H*-imidazo[2,1-*b*]benzothiazole.

Scheme 6. Resonance structure comparisons of tertiary amides and acylammonium salts.

In summary, a Michael enol-lactonization was developed employing cyclic 1,3-diones and coumarin derivatives as Michael donors with commodity acid chlorides as Michael acceptors through acylammonium salt intermediates which were also determined to be formed from enol esters. The process is operationally simple and can be carried out using inexpensive promoters under mild reaction conditions. The methodology presented is useful for the synthesis of fused polycyclic dihydropyranones and also coumarin fused dihydropyranones and dihydropyridinones. NMR studies of the acylammonium salts provide information regarding the extent of β -carbon activation upon reaction of acid chlorides with tertiary amines.

Acknowledgments

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- In conjunction with collaborative computational studies of the Diels-Alder Lactonization process with the Tantillo group (UC Davis) using chiral acylammonium salts (ref. 11), support for reversible acylammonium salt formation at 25 °C when using tertiary amines and pyridine but not BTM has been obtained. These studies will be reported in due course.