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Aluminum Chloride-Mediated Dieckmann Cyclization for the Synthesis of Cyclic 2-Alkyl-1,3-alkanediones: One-Step Synthesis of the Chiloglottones

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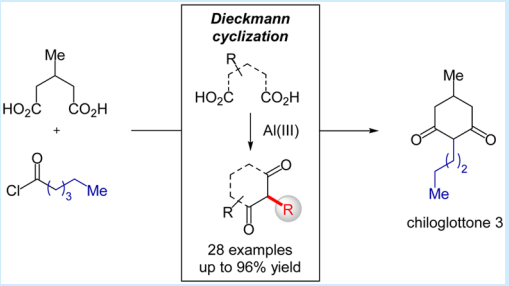
Supporting Information

ABSTRACT: Cyclic 2-alkyl-1,3-alkanediones are ubiquitous structural motifs in many natural products of biological importance. Reported herein is an $AlCl_3$·$MeNO_2$-mediated Dieckmann cyclization reaction of general synthetic utility that enables direct access to complex 2-alkyl-1,3-dione building blocks from readily available dicarboxylic acid and acid chloride substrates. This new strategy enables direct synthetic access to the chiloglottone plant pheromones from commercial material in a single synthetic transformation.



Cyclic 2-alkyl-1,3-alkanediones (**7**, R = alkyl) constitute key synthetic building blocks for the construction of heterocycles,[1] complex molecules, and natural products[2] (Figure 1A). Two of the most prominent examples derived from these structural motifs are the Wieland−Miescher[3] and Hajos−Parrish ketones,[4] **3** and **4**, which represent crucial synthetic intermediates in strategies toward steroid and terpene natural products.[5] Furthermore, cyclic 2,2-dialkyl-1,3-alkanediones can be transformed in desymmetrization approaches to give rise to chiral building blocks for the synthesis of biologically active compounds.[6] A variety of methods have been reported for the synthesis of cyclic 2-alkyl-1,3-alkanediones; however, the vast majority relies on multistep sequences via initial reduction of aromatic precursors **5** that preclude synthetic access to highly functionalized cyclic 1,3-dione building blocks (Figure 1B).[7] Alternative routes rely on base-mediated alkylation procedures that suffer from *O*-alkylation, overalkylation, and ring-cleavage reactions and, in turn, have resulted in the development of alternative alkylation strategies.[8] The most direct approach to 2-alkyl-1,3-alkanedione building blocks reported to date relies on the conversion of dicarboxylic acids with acid chlorides using superstoichiometric Lewis acids as reagents.[9] While this method provided a synthetically appealing route toward the simpler cyclic-1,3-dione congeners,[10,11] subsequent efforts aimed at expanding the substrate scope to more complex motifs[12] were hampered by competing Lewis acid-mediated self-condensation of the requisite acid chlorides to give 4-hydroxy-2-pyrones **18** (Figure 2).[13,14]

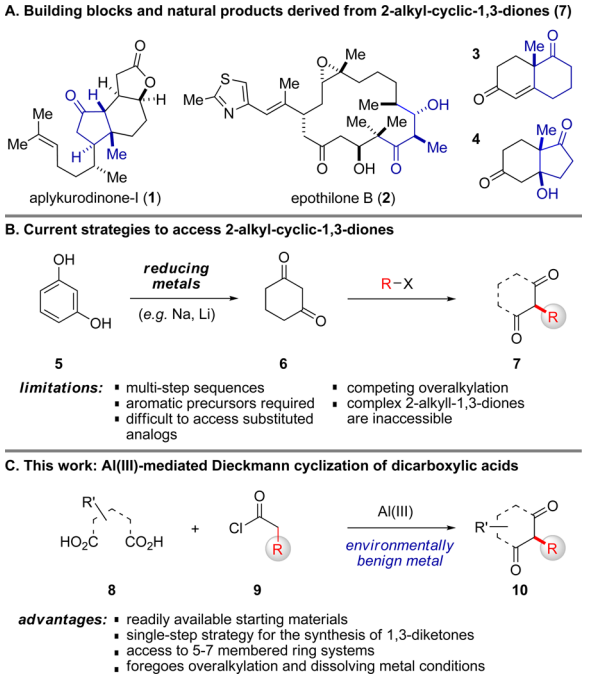


Figure 1. (A) Natural products accessible from cyclic-1,3-dione building blocks. (B) Current strategies to access 2-alkyl-cyclic-1,3-diones. (C) The one-step strategy reported herein.

Specifically, higher-order acid chlorides and substituted dicarboxylic acids did not undergo the desired transformation.[12] During the course of a recent complex molecule synthesis, we were faced with the challenge of rapidly gaining access to highly functionalized cyclic 2-alkyl-1,3-diones, which were inaccessible with previously reported methods. We hypothesized that modulating the Lewis acidity would allow us to subdue the

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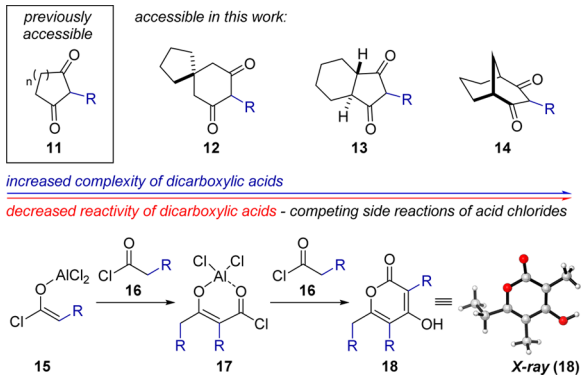
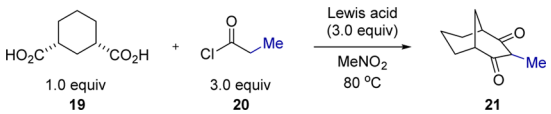


Figure 2. Current limitations of Lewis acid-mediated cyclization of dicarboxylic acids and acid chlorides due to self-condensation of acid chlorides.

inherent tendency for self-condensation of the acid chlorides in order to gain access to more structurally complex 2-alkyl-1,3-dione building blocks. As such, we have developed an efficient and general strategy for Dieckmann cyclization reactions that take advantage of an $AlCl_3$·$MeNO_2$ complex to attenuate the reactivity associated with $AlCl_3$ alone to provide structurally complex and diverse cyclic-1,3-diones (Figure 1C). Importantly, this strategy relies on readily available dicarboxylic acid and acid chloride substrates to afford the desired cyclic-1,3-diones in a single synthetic transformation. Furthermore, this method enables access to bicyclic and spirocyclic motifs as well as products bearing quaternary carbon centers, all of which are otherwise inaccessible from aromatic precursors.

To develop a powerful synthetic strategy toward 2-alkyl-1,3-diones, we initiated our studies with the evaluation of a variety of Lewis acids. Lewis acids were selected based on their established reactivity as Friedel–Crafts catalysts.[15] Specifically, we investigated the conversion of dicarboxylic acid **19** and acid chloride **20** with a variety of Lewis acids (Table 1). Among these, $GaCl_3$ and $FeCl_3$ provided the desired 2-alkyl-1,3-dione **21** in less than 5% yield. The reaction with $ZrCl_4$ proceeded in 15% yield, while $AlCl_3$ proved uniquely effective for this transformation (see Supporting Information (SI) for additional information). Having attributed this unique reactivity to $AlCl_3$, we then moved to optimizing conditions for the Dieckmann cyclization. When **22** and **20** were reacted with $AlCl_3$ in 1,2-dichloroethane (DCE), the desired product **23** was obtained in 28% yield (entry 1, Table 2).

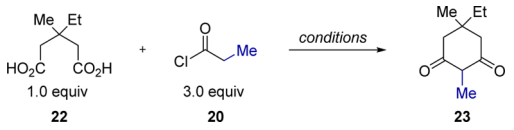
Table 1. Evaluation of Lewis Acids for the Dieckmann Cyclization of Dicarboxylic Acid 19 and Acid Chloride 20[a]



entry	Lewis acid	concentration (M)	time (h)	yield **21** (%)
1	$AlBr_3$	5	3	-
2	BF_3·OEt_2	5	3	-
3	$FeCl_2$	5	3	-
4	$SnCl_4$	5	3	-
5	$GaCl_3$	5	3	<5
6	$FeCl_3$	5	3	<5
7	$SbCl_5$	5	3	<5
8	$TiCl_4$	5	3	<5
9	$ZrCl_4$	5	3	15
10	$AlCl_3$	5	3	55

[a]Conditions: *cis*-1,3-Cyclohexanedicarboxylic acid **19** (1.0 equiv), propionyl chloride **20** (3.0 equiv), and Lewis acid (3.0 equiv) in $MeNO_2$ (5 M) were heated at 80 °C for 3 h. All yields were obtained by GC using dodecane as an internal standard.

Table 2. Optimization of Reaction Conditions for Aluminum Chloride-Mediated Dieckmann Cyclization Reaction



entry	conditions	yield **23** (%)
1	$AlCl_3$ (3.0 equiv), **20** (3.0 equiv), DCE (0.25 M) 80 °C, 3 h	28
2	$AlCl_3$ (3.0 equiv), **20** (3.0 equiv), $MeNO_2$ (0.25 M) 80 °C, 3 h	36
3	$AlCl_3$ (3.0 equiv) in $MeNO_2$ (0.25 M), rt, 1 h then **20** (3.0 equiv), 80 °C, 3 h	59
4	$AlCl_3$ (3.0 equiv), $MeNO_2$ (3.0 equiv) in DCE (0.25 M), rt, 1 h then **20** (3.0 equiv), 80 °C, 3 h	90

Conducting the reaction in nitromethane ($MeNO_2$) under otherwise identical conditions resulted in the formation of **23** in up to 36% yield (entry 2). We hypothesized that the formation of $AlCl_3$·$MeNO_2$ was beneficial for the desired Dieckmann cyclization. Nitromethane is known to moderate the activity of $AlCl_3$ by forming an $AlCl_3$·$MeNO_2$ complex, which is also effective in Friedel–Crafts reactions yet considered a significantly milder alternative to $AlCl_3$.[16] Subsequent efforts focused on optimizing the *in situ* formation of this $AlCl_3$·$MeNO_2$ complex.[17] Specifically, prestirring of **22** and $AlCl_3$ in $MeNO_2$ for 1 h prior to addition of **20** resulted in an increased yield of **23** in 59% (entry 3). We evaluated additives as well as other coordinating solvents for their ability to modulate the reactivity of $AlCl_3$ (see SI for details) and ultimately identified equimolar amounts of $AlCl_3$ and $MeNO_2$ in DCE as the solvent as optimal, providing **23** in 90% yield (entry 4).

This Dieckmann cyclization strategy proved efficient for the synthesis of a variety of 2-alkyl-1,3-diones in up to 96% yield (Scheme 1). It is important to note that rapid keto–enol and enol–enol tautomerization prohibits identification of the major diastereoisomers formed.[18] While these products are represented as 1,3-diones, they primarily exist in an enol form[12] (see X-ray of **28**). Previously reported literature procedures were limited by low yields of products such as **37**, 8% yield, and proved unsuitable for higher-order acid chloride substrates such as heptanoyl and dodecanoyl chloride, resulting exclusively in the formation of polymeric byproducts.[12] When propionyl chloride was converted with dicarboxylic acids bearing distinct substitution patterns, the corresponding 2-methyl-1,3-diones were obtained in up to 96% yield (**24**–**31**, Scheme 1). Cyclic dicarboxylic acids gave rise to spirocycles **28**[19] and **29** as well as bicycles **30** and **21** in up to 91% yield (Scheme 1). Good to excellent yields of the desired 2-ethyl-1,3-diones were obtained with butyryl chloride, resulting in the formation of the desired products in up to 73% yield (**32**–**37**, Scheme 1). Importantly, higher-order acid chlorides such as heptanoyl chloride and dodecanoyl chloride, which were previously incompatible with this method, proved to be viable substrates with our strategy relying on an $AlCl_3$·$MeNO_2$ complex and provided the desired products in up to 71% yield (**38**–**49**, Scheme 1). Unfortunately, further attempts to enhance the complexity (aryl groups,

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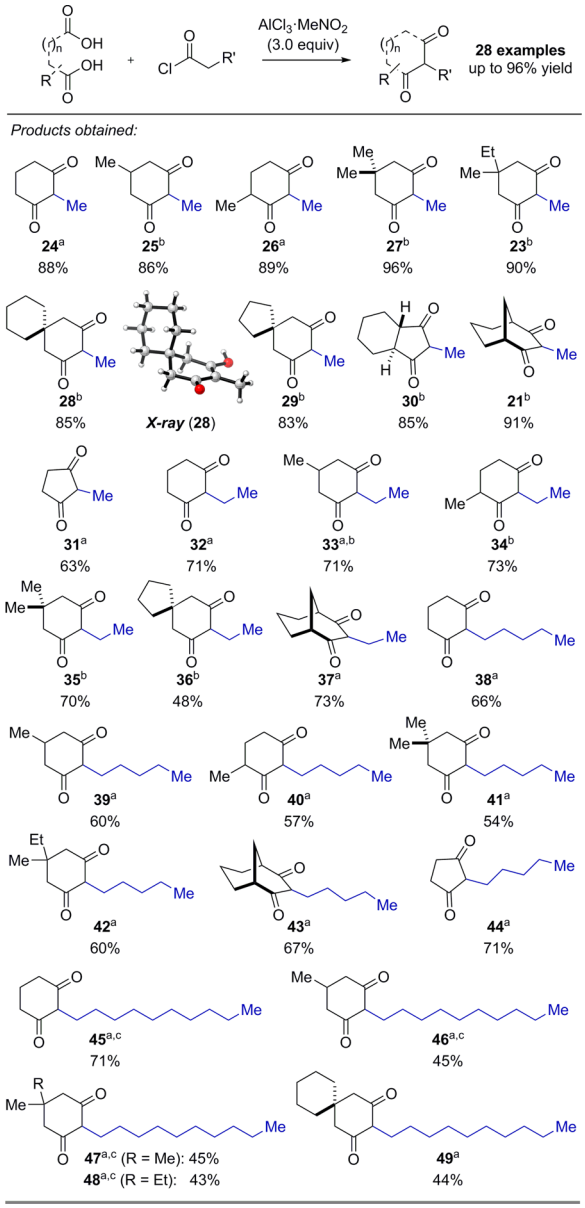
Scheme 1. Cyclic 2-Alkyl-1,3-diones Accessed via the Dieckmann Cyclization of Dicarboxylic Acids[a]



[a]Conditions: (a) $AlCl_3$ (3.0 equiv) and dicarboxylic acid (1.0 equiv) in $MeNO_2$ (0.25 M) were stirred at rt for 1 h. Then acid chloride (3.0 equiv) was added, and the reaction was heated at 80 °C for 3 h; (b) $AlCl_3$ (3.0 equiv), $MeNO_2$ (3.0 equiv), and dicarboxylic acid (1.0 equiv) in DCE (0.25 M) were stirred at rt for 1 h. Then acid chloride (3.0 equiv) was added, and the reaction was heated at 80 °C for 3 h; (c) Reactions were run for 5 h.

heteroatoms, branching) of the cyclic-1,3-dione products proved challenging. Incorporation of aryl rings on either the dicarboxylic acid (e.g., 3-phenylglutaric acid) or acid chloride fragment (e.g., phenylacetyl chloride) provided complex reaction mixtures with the exception of hydrocinnamoyl chloride, which readily underwent Friedel–Crafts acylation to provide 1-indanone. Dicarboxylic acids bearing heteroatoms such as diglycinic acid and *N*-tosyl- and *N*-methyl-iminodiacetic acid failed to undergo the desired Dieckmann cyclization but resulted exclusively in the isolation of the acid chloride self-condensation products, **18** (Figure 2). Lastly, branching at the β-position of the acid chloride did not result in the desired products.[20] Mechanistic investigations are currently underway in order to expand the scope of this reaction. Nonetheless, the protocol described herein attenuates the Lewis acidity of $AlCl_3$ to provide a synthetically useful strategy to 2-alkyl-1,3-diones that were previously challenging to access.[12]

The utility and efficiency of the $AlCl_3$·$MeNO_2$-mediated Dieckmann cyclization strategy reported herein was established in a one-step synthesis of the orchid sex-pheromones, the chiloglottones[21] (Figure 3). These natural products, emitted by

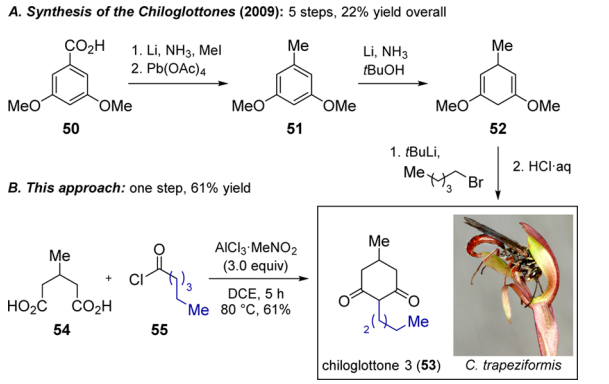


Figure 3. (A) Recent synthetic approach to plant pheromone chiloglottone 3 (**53**) proceeding in 5 synthetic transformations in 22% overall yield. (B) Our one-step synthesis of chiloglottone 3 (**53**) relying on a Dieckmann cyclization strategy of dicarboxylic acids.

both female wasps and orchids (*Chiloglottis trapeziformis*), are employed as a mechanism of sexual deception by orchids to attract male wasps in order to induce pollination. Rapid synthetic access to these plant pheromones is desirable and essential to gain further insight into the evolutionary dynamics of the plant–insect interaction.[21] The first total synthesis of the chiloglottones was reported by Barrow et al., which proceeded in 9 steps and 14% yield overall[22] and was followed by other multistep sequences[23] with the most recent report comprised of two steps.[24] Specifically, the second-generation strategy[22] to the chiloglottones relies on two consecutive Birch reductions of 2,5-dimethoxybenzoic acid (**50**) to ultimately form chiloglottone 3 (**53**) in 22% overall yield (Figure 3). When we converted commercially available dicarboxylic acid **54** and acid chloride **55** in our $AlCl_3$·$MeNO_2$-mediated Dieckmann cyclization strategy, we were able to obtain chiloglottone 3 (**53**) in a single step and 61% yield. This Dieckmann cyclization strategy of dicarboxylic acids described herein takes advantage of the attenuated reactivity of an $AlCl_3$·$MeNO_2$ complex and is the first to tolerate higher-order acid chlorides to allow for the rapid generation of complex, cyclic 2-alkyl-1,3-diones in a single synthetic transformation. The synthetic potential of this new reaction protocol was demonstrated in a one-step synthesis of chiloglottone 3 (**53**) in 61% yield from commercial material. We are currently investigating the mechanism of this reaction in order to enable future reaction optimization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01622.

X-ray data for **18** (CIF)
X-ray data for **28** (CIF)

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Experimental data as well as ^{1}H and ^{13}C NMR spectra for all new compounds prepared here(PDF)

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Notes

The authors declare no competing financial interest.

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(19) Crystallographic data for **28**: $C_{12}H_{18}O_2$ M = 194.26, orthorhombic, space group *Fdd*2, a = 20.1291(4), b = 36.079(3), c = 5.96490(10) Å, V = 4332.0(3) Å^3, ρ_{calcd} = 1.191 Mg/m^{-3}, T = 85(2) K, reflections collected: 16521, independent reflections 1935 (R(int) = 0.0551), R(all) = 0.0277, wR(gt) = 0.0686. CCDC 1457125 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(20) β-Substituted acid chlorides such as 3,3-dimethylbutyryl chloride and isovaleryl chloride primarily provided self-condensation products. While we did not observe any 2-alkyl-1,3-dione species, we did, however, isolate the related 2-acyl-1,3-dione products. This unexpected result prompted us to investigate the mechanism of the reaction. See: Armaly, A. M.; Bar, S.; Schindler, C. S. *Org. Lett.* **2017**, DOI: 10.1021/acs.orglett.7b01623.

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