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Yang Qu
Iowa State University

George A. Kraus
Iowa State University, gakraus@iastate.edu

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Abstract
Both 6-chloro-α-pyrones and 3-chlorobenzopyran-1-ones react with malonates followed by a double decarboalkoxylation to give the corresponding alkyl and alkenyl products.

Keywords
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A flexible route to bioactive 6-alkyl-α-pyrones

Yang Qu and George A. Kraus *

Department of Chemistry, Iowa State University, Ames, IA 50010

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ABSTRACT

Both 6-chloro-α-pyrones and 3-chlorobenzopyran-1-ones react with malonates followed by a double decarboalkoxylation to give the corresponding alkyl and alkenyl products.

Bioactive 6-alkyl-α-pyrones such as 6-pentyl-α-pyrone (**1**)[1], 6-(1-pentenyl)-α-pyrone (**2**)[2] and viridepyronone (**3**)[3] are representative of a growing class of α-pyrones (Fig 1). They exhibit a diverse portfolio of useful activities including the regulation of root architecture, plant growth promotion, and antipathogenic fungal activity. Several researchers have developed routes to **1**, including Dickschat, Schreiber and Pale.[4] The route described herein is strategically distinct from previous approaches in that pyrones **1**-**3** can all be constructed from a common intermediate.

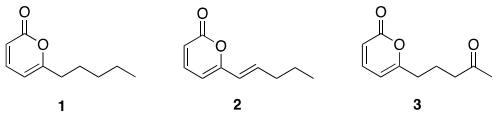
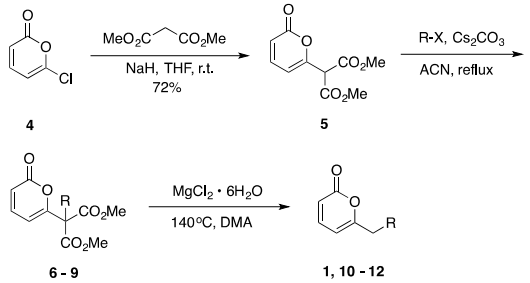


Fig 1. Representative of bioactive 6-alkyl-α-pyrones

The route begins with 6-chloro-α-pyrone (**4**), easily available from commercially available *trans*-glutaconic acid in one step.[5] Although **4** has been reported to undergo Sonogashira reactions with a number of acetylenes, there are no reports of successful additions with organometallic reagents such as cuprates or Grignard reagents.[5,6] Although reports of nucleophilic substitutions of 6-halo pyrones with enolates of carbonyl compounds are rare, Stoltz has recently shown that nucleophilic substitution of the chlorine in **4** with dimethyl malonate affords malonate **5** in good yield.[7] Based on this precedent, we reacted **5** with 1-iodobutane. While the use of NaH in THF led to recovered starting material, the use of cesium carbonate in boiling acetonitrile afforded **6** in 69% isolated yield. The reaction of **6** with standard Krapcho decarboalkoxylation protocols (NaCl, DMSO) led to the recovery of **6**. However, the reaction of **6** with magnesium chloride hexahydrate in dimethylacetamide (DMA) at 140 °C produced pyrone **1** in 82% yield.[8] Normally, S_N2 type decarboalkoxylations of malonates afford the monoacid; however, the stabilization of the anion from the second decarboalkoxylation through the pyrone carbonyl led to **1**. Reaction of **5** with 1-iodohexane followed by double decarboalkoxylation generated **10** in 58% yield

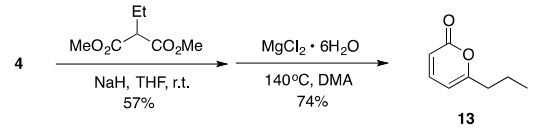


Scheme 1. Preparation of 6-alkyl-α-pyrones.

* Corresponding author. Tel.: +1 515 294 7794; fax: +1 515 294 0105; E-mail address: gakraus@iastate.edu (G.A. Kraus)

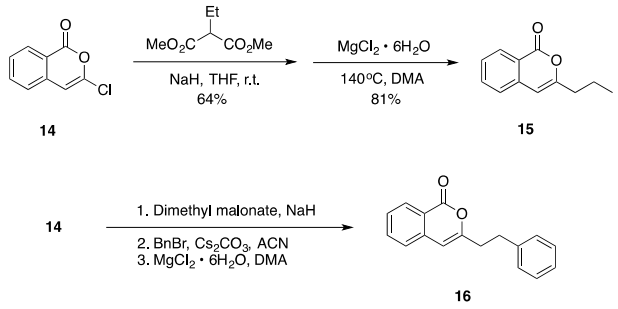
over two steps. Reaction of **5** with allyl bromide and crotyl bromide produced pyrones **11** and **12** in 45% and 51% yields, respectively. Pyrone **12** was treated with chlorobis(cyclooctene)iridium(I) catalyst[9] to isomerize the alkene to generate **2** in 86% yield based on recovered starting material.

Alkyl malonates react with **4** as shown below in Scheme 2. Double decarboalkoxylation then affords pyrone **13** in 43% overall yield. In practice, the crude adduct was taken directly on to the decarboalkoxylation reaction.



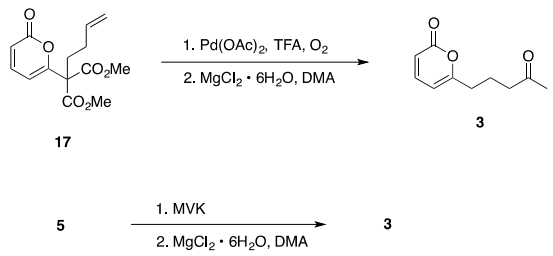
Scheme 2. 6-Chloro-α-pyrone reacts with alkyl malonate.

To demonstrate the scope of this reaction, 3-chlorobenzopyran-1-one (**14**) was synthesized by treating homophthalic acid with $POCl_3$.[10] This compound has been employed in palladium mediated couplings such as the Sonogashira and Suzuki reactions.[10] Using the reaction conditions described in Scheme 1, benzopyran-1-ones **15** and **16**[11] were synthesized in 52% and 57% yields, respectively.



Scheme 3. Synthesis of 3 alkylbenzopyran-1-ones.

Pyrone **17** was readily prepared from the reaction of **5** with cesium carbonate and 4-bromo-1-butene. Wacker oxidation using palladium acetate and oxygen[12] followed by double decarboalkoxylation afforded viridepyronone (**3**) in 48% overall yield. Alternatively, reaction of **5** with methyl vinyl ketone and cesium carbonate followed by double decarboalkoxylation produced **3** in 38% yield over two steps. Viridepyronone showed excellent antifungal activity against several different soil-borne pathogenic fungi. The antifungal activity of this compound was comparable to commercial fungicide Hexaconazole.[3b] Evidente and coworkers have shown in vitro antifungal activity of this compound against *S. rolfsii* at a minimum inhibitory concentration of 196 µg/mL.[3a] To the best of our knowledge, this is the first total synthesis of viridepyronone to be reported.



Scheme 4. Synthesis of viridepyronone 3.

Both 6-Chloropyrone (**4**) and 3-chlorobenzopyran-1-one (**14**) provide direct access to bioactive pyrones. The routes are operationally convenient and proceed in good overall yields. The routes are scalable and will provide quantities of **1**, **2** and **3** for additional biological evaluation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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