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

Yang Qu
Iowa State University

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

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Abstract
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Keywords
6-Chloro-α-pyrone, Bioactive, Malonate, Common intermediate, Double decarboalkoxylation

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

Bioactive 6-alkyl-α-pyrones such as 6-pentyl-α-pyrone (1), 6-(1-pentenyl)-α-pyrone (2) and viridepyronone (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.

The route begins with 6-chloro-α-pyrone (4), easily available from commercially available trans-gluataconic 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 decarboxalkoxylation 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_{N}2 type decarboxalkoxylation of malonates afford the monoacid; however, the stabilization of the anion from the second decarboxalkoxylation through the pyrone carbonyl led to 1. Reaction of 5 with 1-iodohexane followed by double decarboxalkoxylation generated 10 in 58% yield.

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

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(1) catalyst 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 decarboxalkoxylation then affords pyrone 13 in 43% overall yield. In practice, the crude adduct was taken directly on to the decarboxalkoxylation reaction.

![Scheme 2](image)

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

To demonstrate the scope of this reaction, 3-chlorobenzopyran-1-one (14) was synthesized by treating homophthalic acid with POCl₃. This compound has been employed in palladium mediated couplings such as the Sonogashira and Suzuki reactions. Using the reaction conditions described in Scheme 1, benzopyran-1-ones 15 and 16 were synthesized in 52% and 57% yields, respectively.

![Scheme 3](image)


Pyrone 17 was readily prepared from the reaction of 5 with cesium carbonate and 4-bromo-1-butyne. Wacker oxidation using palladium acetate and oxygen followed by double decarboxalkoxylation afforded viridepyronone (3) in 48% overall yield. Alternatively, reaction of 5 with methyl vinyl ketone and cesium carbonate followed by double decarboxalkoxylation 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. Evidente and coworkers have shown in vitro antifungal activity of this compound against *S. rolfsii* at a minimum inhibitory concentration of 196 μg/mL. To the best of our knowledge, this is the first total synthesis of viridepyronone to be reported.

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.

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Supplementary data

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

References and notes