Tetrahedron Letters 58 (2017) 892–893

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Yang Qu, George A. Kraus *

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

ARTICLE INFO

Article history:
Received 7 November 2016
Revised 19 January 2017
Accepted 20 January 2017
Available online 22 January 2017

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

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.

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 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.

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).

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

* Corresponding author.
E-mail address: gakraus@iastate.edu (G.A. Kraus).

http://dx.doi.org/10.1016/j.tetlet.2017.01.063
0040-4039/

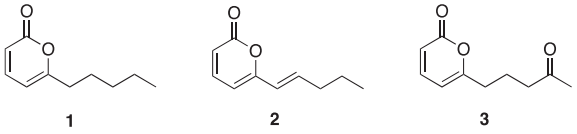
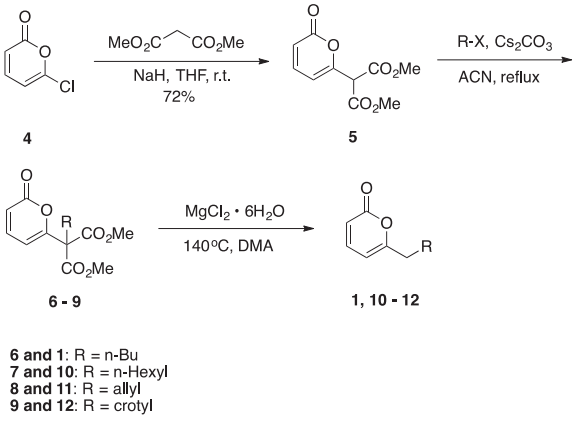
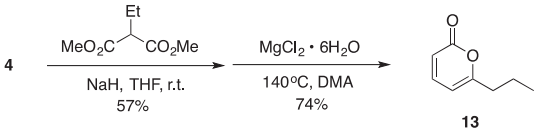


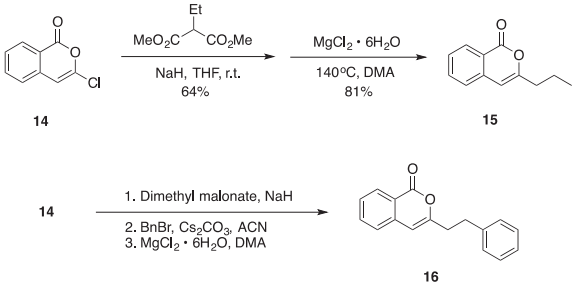
Fig. 1. Representative of bioactive 6-alkyl-α-pyrones.



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



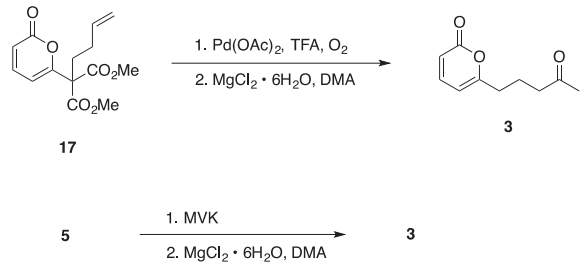
Scheme 2. 6-Chloro-α-pyrone reacts with alkyl malonate.



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

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 (see Scheme 4).

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.



Scheme 4. Synthesis of viridepyronone 3.

Acknowledgments

We thank the NSF Engineering Center for Biorenewable Chemicals (CBiRC) which was awarded NSF grant EEC-0813570 for support of this research.

A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.01.063.

References

1. (a) Mazzei P, Vinale F, Woo SL, Pascale A, Lorito M, Piccolo A. *J Agric Food Chem*. 2016;64:3538;
(b) Garnica-Vergara A, Barrera-Ortiz S, Muñoz-Parra E, et al. *New Phytol*. 2015;209:1496;
(c) Collins RP, Halim AF. *J Agric Food Chem*. 1972;20:437.
2. (a) Rocca J, Tumlinson J, Glancey B, Lofgren C. *Tetrahedron Lett*. 1983;24:1889;
(b) Moss M, Jackson R, Rogers D. *Phytochemistry*. 1975;14:2706.
3. (a) Ahluwalia V, Walia S, Sati OP, et al. *Arch Phytopathol Plant Prot*. 2013;47:1063;
(b) Evidente A, Cabras A, Maddau L, Serra S, Andolfi A, Motta A. *J Agric Food Chem*. 2003;51:6957.
4. (a) Wickel SM, Citron CA, Dickschat JS. *Eur J Org Chem*. 2013;2013:2906;
(b) Luo T, Dai M, Zheng S-L, Schreiber SL. *Org Lett*. 2011;13:2834;
(c) Dombray T, Blanc Aurélien, Weibel JM, Pale P. *Org Lett*. 2010;12:5362.
5. (a) Bellina F, Carpita A, Mannocci L, Rossi R. *Eur J Org Chem*. 2004;2004:2610;
(b) Biagetti M, Bellina F, Carpita A, Rossi R. *Tetrahedron Lett*. 2003;44:607.
6. (a) Fairlamb IJS, O'brien CT, Lin Z, Lam KC. *Org Biomol Chem*. 2006;4:1213;
(b) Fairlamb IJ, Lee AF, Loe-Mie FE, Niemelä EH, O'brien CT, Whitwood AC. *Tetrahedron*. 2005;61:9827.
7. Nelson HM, Stoltz BM. *Org Lett*. 2008;10:25.
8. Gurjar M, Reddy DS, Murugaiah A, Murugaiah S. *Synthesis*. 2000;2000:1659.
9. Ghebreyessus KY, Angelici RJ. *Organometallics*. 2006;25:3040.
10. (a) Dasaradhan C, Kumar YS, Prabakaran K, Khan F-RN, Jeong ED, Chung EH. *Tetrahedron Lett*. 2015;56:784;
(b) Kumar YS, Dasaradhan C, Prabakaran K, et al. *Tetrahedron Lett*. 2015;56:941.
11. Zhang M, Zhang H-J, Han T, Ruan W, Wen T-B. *J Org Chem*. 2015;80:620.
12. Wang Y-F, Gao Y-R, Mao S, et al. *Org Lett*. 2014;16:1610.