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Synthesis of cyercenes and yangonin by a pyrone aldol protocol

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Keywords: Pyrone Yangonin Cyercenes Aldol ABSTRACT

A number of 6-alkenyl pyrones were synthesized using an aldol reaction followed by a tosylate elimination sequence.

Introduction

Substituted pyrones exhibit a broad range of biological activities [1]. Even a simple pyrone such as 6-pentylpyrone is active in promoting plant growth and regulating root architecture. We believe that the polarity (dipole moment of 6.2D) and polarizability of the pyrone moiety plus its potential as a phenol isostere combine to make 4-hydroxy- α -pyrones a productive space for the discovery of new bioactive compounds. Pyrones bearing alkenyl groups at position 6, such as 1–4 display antioxidant activity, anticancer activity, antiviral activity and activity against protein tyrosine phosphatase 1B (Fig. 1) [2–5].

Compounds such as yangonin (1) have been the subject of a number of synthetic approaches [6]. Wittig reactions using pyrone-containing phosphonium salts or condensations using 6-formyl pyrones are the most common ways of producing the diene- and triene-substituted pyrones. These pathways utilize multistep routes with sometimes low overall yields. Kraus and Wanninayake reported the one-pot approach shown in Scheme 1 [7]. This method works well for aromatic aldehydes, providing yangonin in 61% isolated yield. However, it generally does not provide good yields with aliphatic aldehydes. Interestingly, the dehydration of aldol products derived from pyrone anions and aldehydes has been less frequently used. Lyga reported a 14% yield over two steps for a dehydration leading to luteoreticulin [8]. However, both Furstner [9] and Kobayashi [10] have reported elegant syntheses of pyrone trienes using aldol chemistry followed by scandium triflate.

It is important to note that the use of LDA in the aldol addition reaction generates the anion both at the C3 and C7 positions (Scheme 2). Carpenter and coworkers describe that the use of LDA or n-butyllithium generates mostly C3 substitution [11]. By treating 4-methoxy-6-methyl-2-pyrone with n-butyllithium or LDA and subsequently treating the anionic mixture with trimethylsilylchloride, they achieved 3-trimethylsilylpyrone. To combat this issue, we used lithium hexamethyldisilazane (LHMDS), which generated the anion at C7 only. No C3 substitution product was observed when using LHMDS. To the best of our knowledge, Kobayashi was the first to report the use of LHMDS with simple pyrones [10]. Hsung reported clever applications of the dianion of triacetic acid lactone to achieve similar products [12].

We synthesized pyrone **7** as a model system and evaluated mild elimination procedures. We used the adduct of triphenyl phosphite and methyl iodide, a reagent that has been used to prepare 1,3,5-hexatriene, a labile triene, from the dienol [13]. Unfortunately, the reaction with 7 produced a complex mixture containing little dehydration product. The selenoxide elimination is an established method to generate transalkenes with high selectivity. Zoretic has shown that orthonitrophenyl selenocyanate and tributylphosphine can convert an alcohol into the corresponding selenide at ambient temperature [14]. We found that the more readily available phenylselenocyanate gave comparable yields. As shown in Scheme 3, the reaction with **7** produced the desired diene **8** [7] in 61% yield over two steps.

We prepared pyrones **9** and **10** using this aldol/selenoxide procedure (Scheme 4). Although the eliminations were successful, the yields using the selenium chemistry were modest.

When we extended the selenium elimination chemistry to make yangonin, the isolated yield was only 38%. Since yangonin was necessary for a number of ongoing studies, including a collaboration on organic corrosion inhibitors, we needed a more effective route. We revisited the elimination reaction using tosyl chloride/DMAP instead of the mesyl chloride/LDA conditions used by Lyga. The results are shown below in Scheme 5 (See Scheme 6 and 7).

The cyercenes 2a and 2b are pyrones isolated from the ascoglossan

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Fig. 1. Alkenyl pyrone natural products.



Scheme 1. Synthesis of styrenyl pyrones.



Scheme 2. Anion generation at C3 or C7 when using different lithium amide bases.



Scheme 3. Selenoxide elimination to achieve 6-alkenyl pyrones.



Scheme 4. Synthesis of alkenyl pyrones 9 and 10.



Scheme 5. Synthesis of Yangonin.

mollusk Cyerce cristallina and have been synthesized using Wittig reactions and organometallic coupling reactions [15]. Beginning from known pyrone **12** [16] an aldol reaction using 2-methyl-2-butenal afforded aldol **13** which could be converted into **2a** in 61% yield with TsCl/DMAP. Similarly, reaction of the anion of **12** with 2-methyl-2-pentenal provided the aldol product which could be converted into **2b** in



Scheme 6. Synthesis of Cyercenes.



Scheme 7. Synthesis of pyrone 15.

54% yield. The conditions described in Scheme 1 did not provide 2a.

An increasing number of natural products have been isolated that bear the 2-methoxy-4-pyrone subunit [17]. As an entry into this system, we converted pyrone 14, prepared in one step from triacetic acid lactone, into 15 in 33% yield over two steps using the conditions developed above.

The synthesis of various natural products and natural product analogs has been achieved using a practical, scalable two-step procedure. Both alpha-pyrones and gamma-pyrones participate in this procedure.

CRediT authorship contribution statement

Kyle Podolak: Conceptualization, Supervision, Conducted the research. **George A. Kraus:** Conceptualization, Supervision, Writing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2021.100219.

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