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Synthesis of polyhydroxylated xanthones via acyl radical cyclizations

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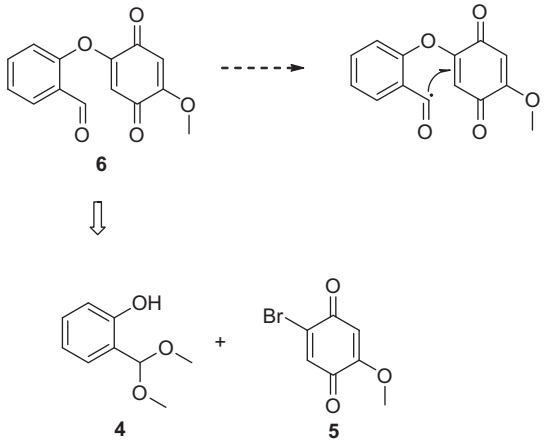
ABSTRACT

2-Formylphenoxy quinones can be converted into xanthones via an acyl radical intermediate with NBS and AIBN.

Xanthones are found in many plants, including *Hypericum* and *Prunella* species. Many xanthones bearing hydroxyl substituents exhibit valuable biological activity.[1] Daviditin A (**1**) preserves endothelial dysfunction elicited by lysophosphatidyl choline (Fig. 1). The protective effect of daviditin A on the endothelium is related to reduction of asymmetric dimethylarginine concentration.[2] Xanthone **2** was shown to relax the corpus cavernosal smooth muscle by 97% compared to Viagra.[3] Bellidifolin (**3**) improved insulin resistance by enhancing insulin signaling.[4]

Because of the diverse biological activities of xanthones, several approaches have been reported.[5] Of these methods, Friedel–Crafts acylation/cyclization protocols[6] are the most commonly used methods. However, synthetic methods for highly hydroxylated xanthones are limited. Recently, strategies employing photochemistry,[7] benzyne addition,[8] and directed metallation[9] have been reported. We report herein a synthesis of polyhydroxylated xanthones employing acyl radical intermediates.



Scheme 1. Strategy for xanthone synthesis.

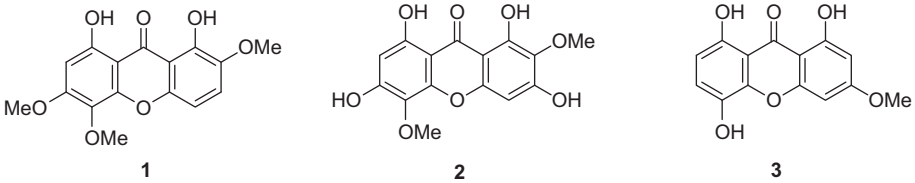


Figure 1. Structures of xanthones.

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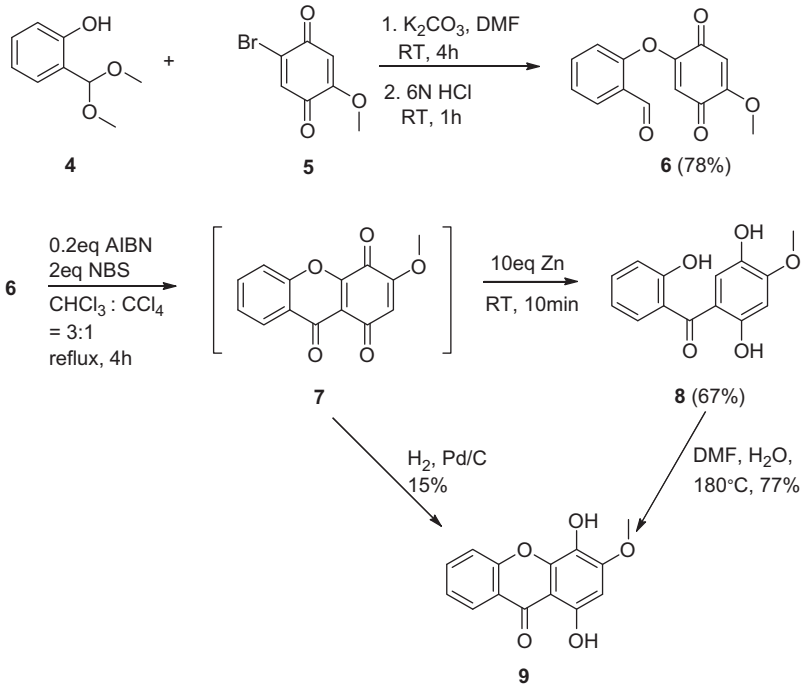


Scheme 2. Synthesis of xanthone **9**.

We recently reported that radicals generated by decarboxylation of an acid with persulfate underwent intramolecular cyclization to a quinone, resulting in a direct synthesis of Bauhinoxepin J.[10] If an acyl radical could be generated from **6**,[11] the cyclization could lead to a direct synthesis of xanthones (Scheme 1). The quinone **6** can be synthesized by a coupling reaction of acetal **4** with bromoquinone **5**.

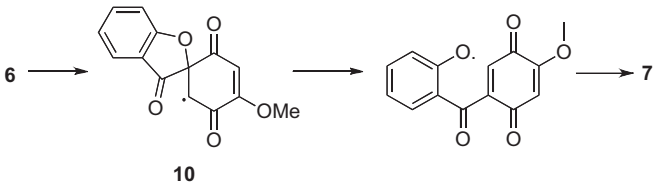
We first tried directly coupling salicyladehyde with bromoquinone **5** to generate quinone **6**, but the reaction failed. After conversion of salicyladehyde to acetal **4**,[12] the reaction of acetal **4** with bromoquinone **5** and K_2CO_3 in DMF followed by HCl hydrolysis afforded quinone **6** in 78% yields (Scheme 2). To the best of our knowledge, there have been no reports for the synthesis of xanthones from quinones such as **6**. Initially, we irradiated quinone **6** under conditions where an intramolecular hydrogen atom abstraction via an excited state quinone could lead to an acyl radical. Unfortunately, only starting material was recovered. We next attempted to generate the acyl radical through hydrogen atom abstraction using the diradical of benzophenone, a strategy we had used successfully to generate acylhydroquinones.[13] This approach also failed.

Cheung and later Marko reported that aryl aldehydes could be converted to acid bromides with NBS.[14] Although this transformation has not been extensively studied, this reaction likely proceeds through an acyl radical intermediate. Treatment of quinone **6** with NBS and a catalytic amount of AIBN in $CHCl_3$ and CCl_4 produced xanthone **7**. A number of experiments were conducted to optimize the transformation and it was found that two equivalents of NBS and 0.2 equiv of AIBN were necessary to achieve good conversion. Unfortunately, xanthone **7** was not stable to column chromatography. The xanthone **7** was reduced by catalytic hydrogenation to generate xanthone **9**, albeit in only 15% yield after two steps. The structure of xanthone **9** was confirmed by X-ray spectroscopy. Reduction of xanthone **7** with zinc in acetic acid afforded benzophenone **8** in 67% yields after two steps, whose structure was also determined by X-ray spectroscopy. This appears to be the first example of xanthone cleavage under reductive conditions. Moreover, this result was unexpected and suggests that production of xanthone **7** presumably arises from a spirocyclic intermediate such as **10** that would result from a 5-exo-trig radical cyclization. Elimination of the phenoxide radical followed by cyclization and oxidation provides a route to **7** (Scheme 3). Attempts to isolate intermediates in the rearrangement by conducting the reaction using only one equivalent of NBS produced starting material plus a reduced yield of **7**. It is possible that the mechanism involves a 6-endo closure followed by a rearrangement. Benzophenone **8** could be readily cyclized to form xanthone **9** by heating in aqueous DMF at 180 °C for 16 h.[7] Xanthone **9** is produced in an overall yield of 40%. Interestingly, benzophenone **8** is a natural product isolated from *Dalbergia cochinchinensis*.[15]

This procedure was applied to other bromoquinones. The results in Table 1 show the quinone precursors that were synthesized. The overall yields are in the range of 52–78%.

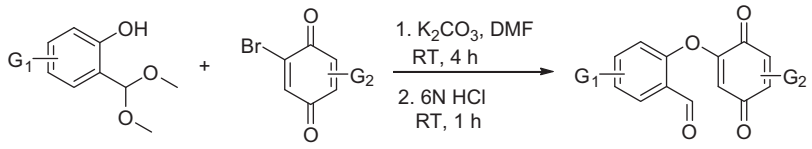
The xanthones in Table 2 were prepared from the corresponding quinones by cyclization with AIBN and NBS, reduction with zinc, and cyclization in DMF/water. The xanthone in entry 2 is a natural product isolated from *Centaurium erythraea*[16] that had not previously been synthesized. The overall yields for different xanthones are 40% (entry 1), 36% (entry 2), 31% (entry 3), 29% (entry 4), and 30% (entry 5).

In summary, the first synthesis of xanthones by acyl radical chemistry has been achieved. Two natural products were synthesized. This novel approach will permit the direct synthesis of novel polyhydroxylated xanthones.



Scheme 3. Proposed mechanism for the production of **7** from **6**.

Table 1
Reaction of **4** with **5** to generate quinone **6**



4 **5** **6**

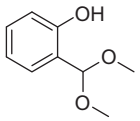
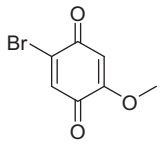
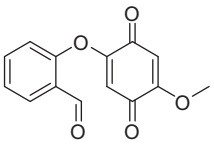
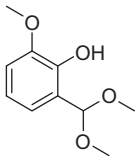
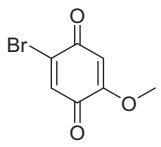
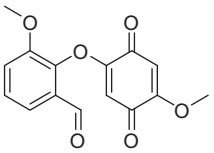
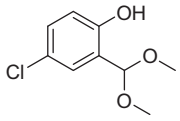
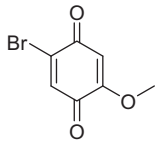
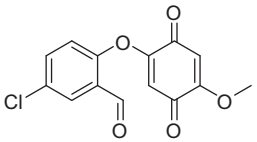
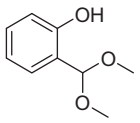
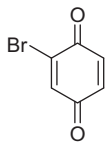
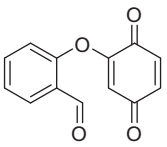
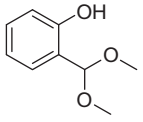
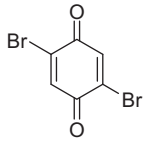
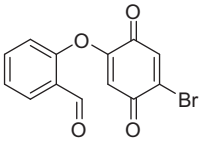
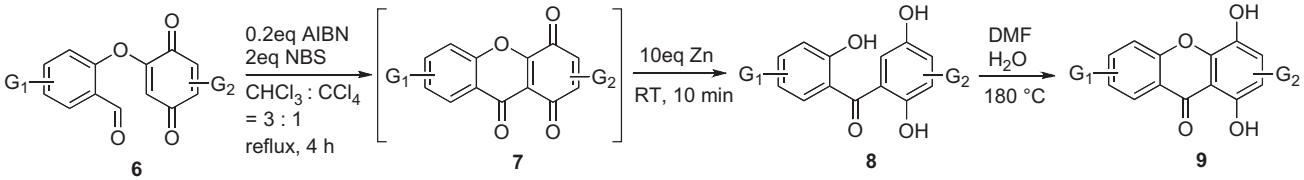
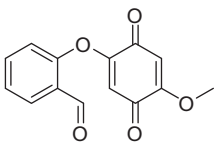
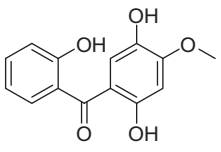
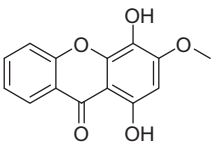
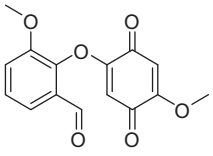
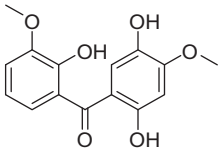
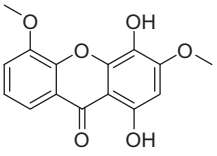
Entry	4	5	6	Isolated yield (%)
1				78
2				76
3				73
4				58
5				52

Table 2
Reaction of quinone **6** to generate **8** and xanthone **9**

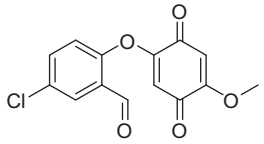
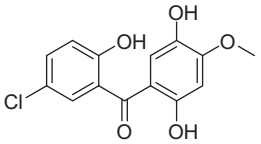
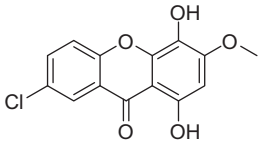
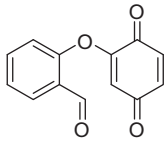
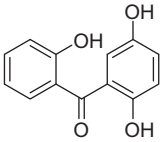
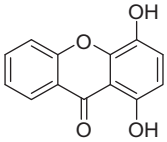
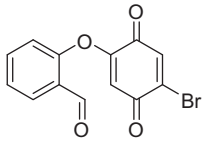
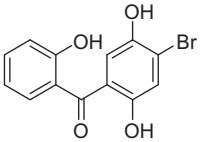
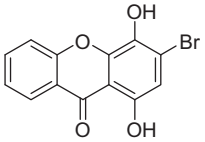


6 **7** **8** **9**

Entry	6	8[a]	Isolated yield (%)	9[b]	Isolated yield (%)
1			67		77
2			65		72

(*continued on next page*)

Table 2 (*continued*)

Entry	**6**	**8**[a]	Isolated yield (%)	**9**[b]	Isolated yield (%)
3			60		70
4			68		73
5			75		77

[a] Entry 1 is a natural product isolated from *Dalbergia cochinchinensis*.
[b] Entry 2 is a natural product isolated from *Centaurium erythraea*.

Acknowledgment

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