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A New Regiospecific Preparation of Xanthones

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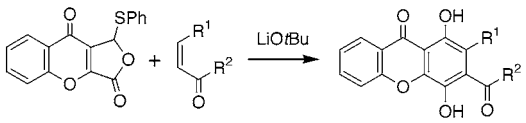
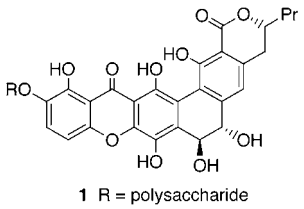
ABSTRACT



Condensation of a benzopyranonphthalide with Michael acceptors provides an efficient, general method for regiospecific preparation of xanthones as well as linear and angular polycyclic aromatic systems containing a xanthone fragment.

There are numerous naturally occurring xanthones[1] and also a number of natural products with a xanthone fragment such as bikaverin,[2] cervinomycins,[3] lysolypin,[4] citreamicins[5] and FD-594[6] (**1**) (Figure 1).

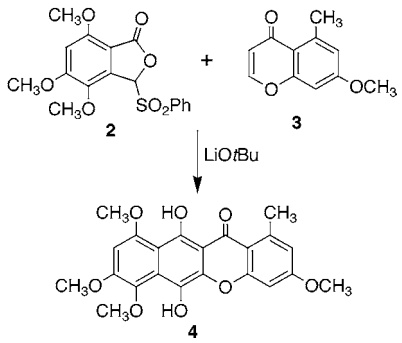


1 R = polysaccharide

Figure 1.

Previously, we reported directed annelation methodology for regiospecific preparation of the linear xanthone **4** based on condensation of the phthalide **2** with the benzopyranone **3** (Scheme 1).[7] While this protocol provided an efficient route to the linear xanthone bikaverin, attempted extension of the methodology to angular polycyclic aromatic systems was not successful.[8]

Scheme 1



2 **3** **4**

Our continuing interest in this class of compounds led us to devise a new approach for regiospecific preparation of xanthones and xanthone-containing polycyclic aromatic systems. This plan, shown in Scheme 2, was based on the

(1) For reviews see: Mandal, S.; Das, P. C.; Joshi, P. C. *J. Indian Chem. Soc.* **1992**, *69*, 611−636. Murray, R. D. H. *Aromat. Heteroaromat. Chem.* **1978**, *6*, 258−281.

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(3) Nakagawa, A.; Omura, S.; Kushida, K.; Shimizu, H.; Lukacs, G. *J. Antibiot.* **1987**, *40*, 301−308.

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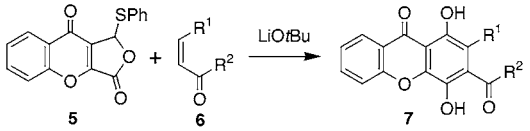
Scheme 2

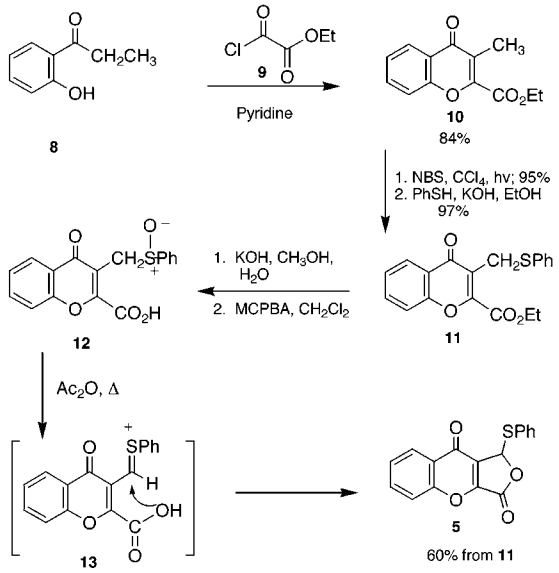


expectation that the benzopyranonephthalide **5** might undergo condensation with Michael acceptors **6** to afford **7**.

If successful, this approach would provide an alternative and ultimately more general approach to the preparation of xanthones and extended aromatic systems with a xanthone fragment. An immediate question was whether **5** would exhibit the desired condensation chemistry.

To explore this point, we prepared the benzopyranonephthalide **5** (Scheme 3). The procedure reported by

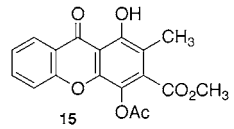
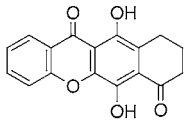
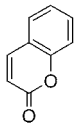
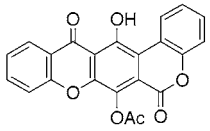
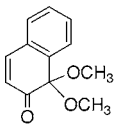
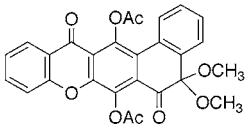
Scheme 3



Zagorevskii et al.[9] provided an 84% yield of the chromanone **10** from *o*-hydroxypropiophenone **8** and ethyl chlorooxoacetate **9**. NBS bromination of **10** gave the bromomethyl intermediate (95%), which on reaction with thiophenoxide afforded the thiophenylated product **11**. Hydrolysis of the ester followed by MCPBA oxidation gave the sulfoxide acid **12**. As expected, Pummerer reaction of **12** in acetic anhydride resulted in intramolecular trapping of the sulfenium intermediate **13**, directly providing the thiophenyl-substituted benzopyranonephthalide **5**.

With **5** in hand, we explored its condensation chemistry. Treatment of **5** with LiOtBu in THF at −78 °C afforded a deep blue-colored solution of the anion. Reaction of the anion with methyl crotonate (**14**) and then quenching the reaction with acetic anhydride[10] afforded an 88% yield of the xanthone **15** (Table 1). Similarly, condensation of **5** with

Table 1. Products and Yields from Condensation of the Benzopyranone-phthalide **5** with Various Michael Acceptors[a]

entry	acceptor	product	yield (%)
1	$CH_3CH{=}CHCO_2CH_3$ (**14**)	 (**15**)	88
2	 (**16**)	 (**17**)	82
3	 (**18**)	 (**19**)	67
4	 (**20**)	 (**21**)	78

[a] Reaction of **5** with **16** was not quenched with Ac_2O.

cyclohexenone **16** provided an 82% yield of the expected linear benzoxanthanone **17**. We next investigated the potential of the reaction for angular polycyclic aromatic synthesis. Condensation of **5** with coumarin (**18**) gave a 67% yield of the product **19**. Recently, we reported the use of *ortho*-quinonemonoketals as acceptors in phthalide condensations.[11] Condensation of the *ortho*-quinonemono-ketal **20** with **5** afforded a 78% yield of the angular polycyclic product **21**.

In summary, this annelation provides a general, high-yielding route to not only xanthones but also xanthone-containing polycyclic aromatic systems. We expect that this methodology will be useful for the preparation of angular polycyclic aromatic natural products and currently are exploring this possibility.

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(10) Acetylation prevents oxidation of the initially formed product.

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