Divergent Approach to Flavones and Aurones via Dihaloacrylic Acids. Unexpected Dependence on the Halogen Atom

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Abstract

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Divergent Approach to Flavones and Aurones via Dihaloacrylic Acids. Unexpected Dependence on the Halogen Atom

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ABSTRACT

The reaction of phenols with 7a led to the synthesis of aurones, while the reaction of phenols with 7b led to the synthesis of flavones. Flavones are natural products common to many plant genuses.1 Examples of this important family include flavones 1−5 shown in Figure 1. Natural and synthetic flavones exhibit a range of biological activity, including anti-inflammatory,2 anticancer,3 and antioxidant4 activity. As a result, a number of useful synthetic methods have been reported. The majority of these methods falls into the category of either oxidative cyclization of various substituted 2'-hydroxychalcones or cyclodehydration of substituted 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones.5,6

As part of an interdisciplinary effort to understand the modes of action of components of botanical dietary supplements,7 we needed to develop a convergent synthesis of flavones that would be amenable to the creation of functional libraries. In view of the ready availability of substituted aryl boronic acids, we examined the disconnection shown in Figure 2.

The synthesis began with the coupling of commercially available phenol 6a with 3,3-dibromoacrylic acid (7a)8 using DCC and DMAP in 71% yield.9 A Fries rearrangement using aluminum chloride in 1,2-dichloroethane produced ketone 10 in 41% yield, accompanied by products derived from Fries rearrangement and demethylation. Cyclization of 10 with dilute sodium hydroxide in THF afforded a bromoketone, originally assigned as 11a. However, Suzuki coupling with

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phenylboronic acid (8a) provided a compound whose NMR spectrum was different from an authentic sample of 4 prepared by the literature method.\textsuperscript{10} After considering alternate structures, the structure of 11a was revised to 11b. This implies that the Suzuki coupling led to aurone 12a, and this was confirmed. Using the same protocol, aurones 12b and 12c were produced in 81% and 80% yields, respectively, and were confirmed by comparison with literature spectra (Scheme 1).\textsuperscript{11}

While this chemistry was being pursued, a parallel series of reactions was conducted using 3,3-dichloroacrylic acid (7b),\textsuperscript{12} in part because its preparation was more conducive to scale up. As shown in Scheme 2, esters 13a and 13b underwent Fries rearrangements to afford ketones 14a and 14b in 40% and 60% yields, respectively. The dichloro ketones were treated with dilute base to generate chromones 15a and 15b in good yields. Although the Suzuki reaction is more commonly conducted with aryl bromides or iodides,\textsuperscript{13} the reaction of 15b with boronic acid 8a afforded flavone 1 in 74% yield.\textsuperscript{14} Our NMR spectrum matched the spectrum of an independently synthesized sample.\textsuperscript{10} In a similar manner, flavones 2–5 were synthesized in good yields and compared to literature standards.\textsuperscript{10,15a–c}
The rationale for the remarkable divergence remains unclear. We speculate that intramolecular cyclization of 10 might be slow relative to dehydrobromination to a bromo acetylenic ketone. The bromo acetylenic ketone could then cyclize to 11b, the precursor to the aurones.

In summary, we have devised a synthetic route which is direct and proceeds in good overall yield. This procedure will permit the synthesis of both natural and synthetic flavones and aurones.

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Supporting Information Available: Representative experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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