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

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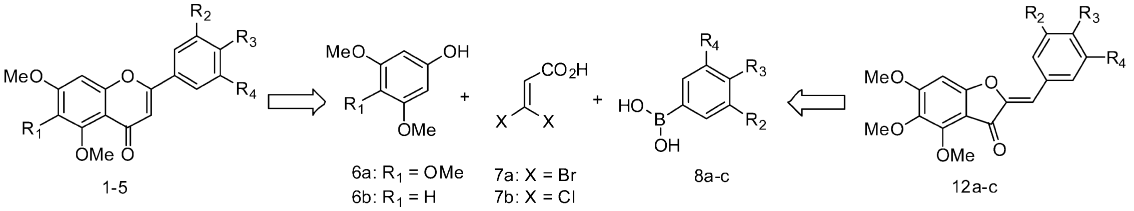
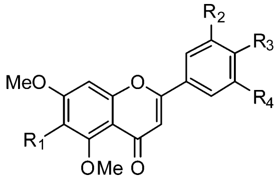
ABSTRACT



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 antioxidant[4] 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.



1. $R_1 = R_2 = R_3 = R_4 = H$
2. $R_1 = R_2 = R_4 = H$, $R_3 = OMe$
3. $R_1 = R_2 = H$, $R_3 = R_4 = OMe$
4. $R_1 = OMe$, $R_2 = R_3 = R_4 = H$
5. $R_1 = R_3 = OMe$, $R_4 = R_2 = H$

Figure 1. Structures of flavones.

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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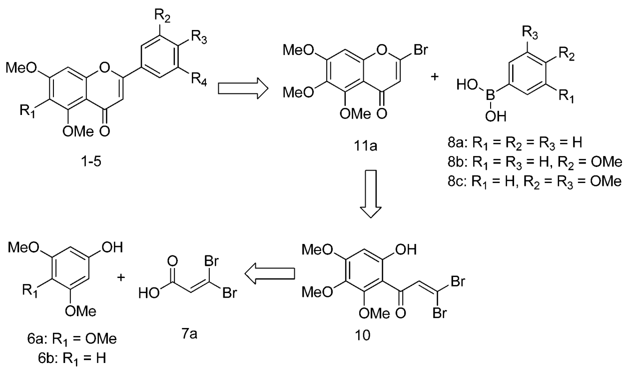
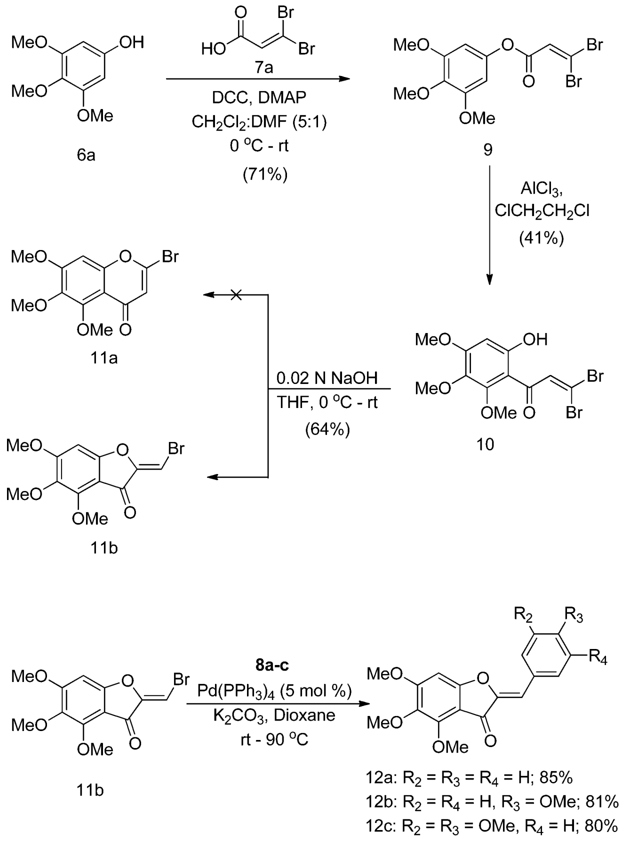


Figure 2. Retrosynthetic analysis.

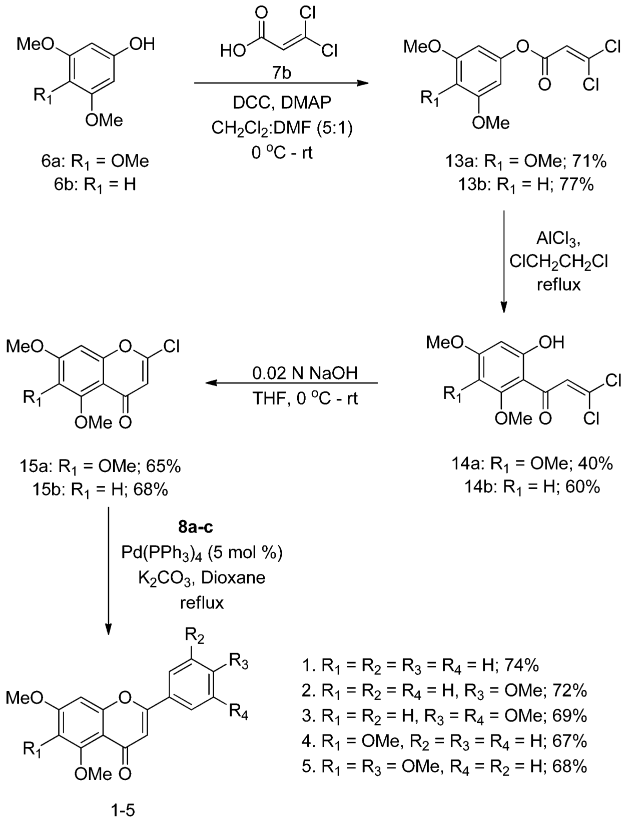
phenylboronic acid (**8a**) provided a compound whose NMR spectrum was different from an authentic sample of **4** prepared by the literature method.[10] After considering alternate structures, the structure of **11a** was revised to **11b**. This implies that the Suzuki coupling led to aurone **12a**, 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).[11]

While this chemistry was being pursued, a parallel series of reactions was conducted using 3,3-dichloroacrylic acid (**7b**),[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,[13] the reaction of **15b** with boronic acid **8a** afforded flavone **1** in 74% yield.[14] Our NMR spectrum matched the spectrum of an independently synthesized sample.[10] In a similar manner, flavones **2**−**5** were synthesized in good yields and compared to literature standards.[10,15a−c]

Scheme 1. Synthesis of Aurones



Scheme 2. Synthesis of Flavones



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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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