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Development of a general approach to the synthesis of a library of isoflavonoid derivatives

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ABSTRACT

Isoflavonoids are a class of organic compounds that act primarily as antioxidants. They are produced almost exclusively by various members of the bean family including soybeans, tofu, peanuts, chick peas, and alfalfa. The antioxidant characteristics that isoflavonoids exhibit help hinder the progression of certain cancers, primarily breast, prostate, and colon cancer. We have developed a three-five step synthesis for obtaining a suite of isoflavonoid derivatives. The synthesis involves an enamine formation, a ring closure and halogenation, a Suzuki coupling, and finally a global deprotection to obtain the respective isoflavonoid derivatives.

Flavonoids, also commonly referred to as bioflavonoids in the media, are a class of plant secondary metabolites that are most commonly known for their antioxidant activity.[1] These organic compounds are widely distributed in plants satisfying a variety of functions, including the production of a yellow or red/blue pigmentation in flowers as well as protection from attack by microbes and insects.[2] The vast abundance of flavonoids, their variety, and their relatively low toxicity compared to that of other active plant compounds allow for animals, including humans, to ingest significant quantities in their diet without any adverse side effects.[2] Consumers and the food industry have become increasingly interested in flavonoids for their medicinal properties,[2] especially their potential application in the prevention of cancers[3–5] and cardiovascular disease.[2,6] A number of health benefits related to the consumption of fruits, vegetables, teas, or even red wines have been attributed to these compounds rather than other known nutrients and vitamins.[2]

The flavonoid class is divided into three main groups: flavonoids, isoflavonoids, and neoflavonoids. These groups consist of relatively abundant natural products primarily derived from 2-phenylchromen-4-one (flavonoid), 3-phenylchromen-4-one (isoflavonoid), and 4-phenylcoumarin (neoflavonoid), respectively (Fig. 1). Derivations include reduction of the double bond between the second and third carbon (flavanones), reduction of the keto group (flavanols), and hydroxylation at various positions. The resulting derivatives can be classified into ten groups: chalcones, flavanones, flavones, flavonols, anthocyanidins (flavylium cations), flavan 3-ols (catechins), flavan 3,4-diols (proanthocyanidins), biflavonoids and oligomeric flavonoids, isoflavonoids, and the aurones.

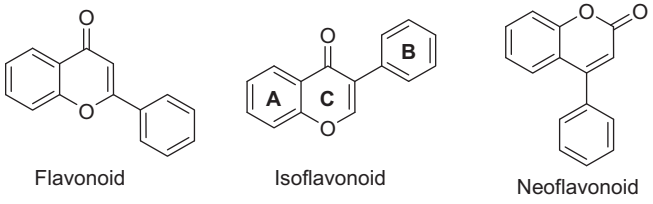

Figure 1. Structures of flavonoids, isoflavonoids, and neoflavonoids.

Despite the vast array of studies investigating isoflavonoids, the exact mode of their biological action still remains undetermined. The synthesis of radiolabeled derivatives has received attention in recent years as they can function as internal standards to address the absorption, distribution, metabolism, and excretion (ADME) questions.[7,8] Key to this approach is the development of isotopically pure standards, differing by at least three mass units from the unlabeled analogue, where the inherent mass difference between the labeled and unlabeled derivatives allows for metabolic studies of isoflavonoids to be conducted through the use of mass spectrometry-based methods such as LC-MS and GC–MS. To date, the development of deuterium and carbon-13-based daidzein

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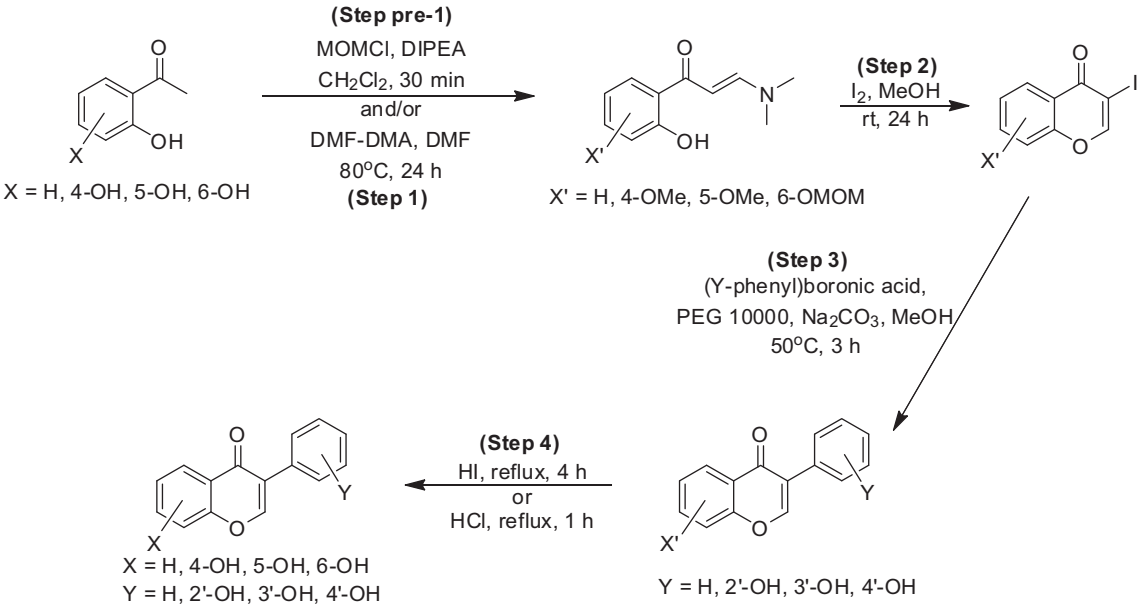

Scheme 1. Synthetic route for library of isoflavonoids (**1**–**16**).

Table 1
Products and yields of isoflavonoid derivatives

	$(HO)_2B$	$(HO)_2B$ OH	$(HO)_2B$ OH	$(HO)_2B$ OH
OH	**1** Step 1 (99%) Step 2 (98%) Step 3 (95%)	**2** Step 1 (99%) Step 2 (98%) Step 3 (59%)	**3** Step 1 (99%) Step 2 (98%) Step 3 (87%)	**4** Step 1 (99%) Step 2 (98%) Step 3 (92%)
HO OH	**5** Step 1 (89%) Step 2 (81%) Step 3 (93%) Step 4 (94%)	**6** Step 1 (89%) Step 2 (81%) Step 3 (66%) Step 4 (90%)	**7** Step 1 (89%) Step 2 (81%) Step 3 (84%) Step 4 (92%)	**8** Step 1 (89%)[9] Step 2 (81%)[9] Step 3 (98%)[9] Step 4 (89%)[9]
HO OH	**9** Step 1 (43%) Step 2 (81%) Step 3 (74%) Step 4 (90%)	**10** Step 1 (43%) Step 2 (81%) Step 3 (60%) Step 4 (88%)	**11** Step 1 (43%) Step 2 (81%) Step 3 (76%) Step 4 (96%)	**12** Step 1 (43%) Step 2 (81%) Step 3 (85%) Step 4 (94%)
OH OH	**13** Step pre-1 (95%) Step 1 (99%) Step 2 (81%) Step 3 (91%) Step 4 (93%)	**14** Step pre-1 (95%) Step 1 (99%) Step 2 (81%) Step 3 (62%) Step 4 (95%)	**15** Step pre-1 (95%) Step 1 (99%) Step 2 (81%) Step 3 (77%) Step 4 (94%)	**16** Step pre-1 (95%) Step 1 (99%) Step 2 (81%) Step 3 (86%) Step 4 (88%)

[Step pre-1 = MOM protection; Step 1 = Enamine formation or enamine formation/methylation; Step 2 = Ring closure/iodination; Step 3 = Suzuki coupling; Step 4 = Deprotection].

probes have received the most attention.[7,8] Herein, we outline a general approach to a synthesis of a library of isoflavonoids that could be used in labeling and other syntheses.

Recently we demonstrated the total synthesis of daidzein[9,10] and genistein[11] from acetophenone derivatives in four and five steps, respectively. Our synthesis of daidzein involved the formation of the enamine from its corresponding acetophenone using *N,N*-dimethylformamide dimethylacetal (DMF-DMA). This had the serendipitous effect of also protecting the 4-hydroxyl as its methyl ether. We have subsequently explored this latter event in a greater detail.[12] Unfortunately, when we attempted this with the 2,4,6-trihydroxyacetophenone, we were unsuccessful and thus needed to employ MOM-protection to ultimately obtain the desired genistein. In light of this, we decided to initially attempt to synthesize our library of isoflavonoids in a similar route as we had for daidzein and thus only employ MOM-protection if necessary (Scheme 1).

With this in mind we began with the synthesis of the simplest of all the isoflavonoids (Table 1), 3-phenylchromen-4-one (**1**). Indeed, when 2-hydroxyacetophenone was reacted with DMF-DMA the corresponding enamine was obtained in 99% yield (**Step 1**). Similarly, when we performed the one-pot, two-step ring closure and iodination via addition of I_2 in MeOH, the 3-iodochromone was produced in near quantitative yield (**Step 2**). As with both daidzein[9,10] and genistein,[11] we utilized a green approach for the Suzuki coupling demonstrated by Liu et. al.[13] By employing poly(ethylene glycol) 10,000 (PEG 10,000) as the ligand, along with $Pd(OAc)_2$, Na_2CO_3 in MeOH, and phenylboronic acid, we performed the cross-coupling reaction to obtain phenylchromen-4-one (**1**) in 95% yield (**Step 3**). To our delight, our synthetic route also allowed for the use of alternate arylboronic acids to produce other isoflavonoid derivatives. Thus, using 2-, 3-, or 4-hydroxyphenylboronic acid afforded 2′-hydroxyisoflavonoid (**2**: 59%), 3′-hydroxyisoflavonoid (**3**: 87%), and 4′-hydroxyisoflavonoid (**4**: 92%), respectively. Of note, as the hydroxyl group moves further away from the reactive boronic acid site the yield of the coupling reaction increased. This trend was also observed for the other members of the library (Table 1).

We next focused on the introduction of hydroxyls on Ring A of the isoflavonoid (Fig. 1). We decided to use commercially available acetophenones, including 2,3-, 2,4-, 2,5-, and 2,6-dihydroxyacetophenone; however, we ultimately did not utilize the 2,3-dihydroxyacetophenone variant as we found this to be too cost prohibitive. Therefore, as with our synthesis of daidzein, we began with the enamine formation/O-methylation with DMF-DMA on the 2,4-dihydroxyacetophenone (**Step 1**). After the one pot-two step ring closure and iodination (**Step 2**), we were in the position to perform the cross-coupling with phenylboronic acid as well as with its 2-, 3-, and 4-hydroxy derivative (**Step 3**). In all four examples we successfully synthesized the 4-methoxyisoflavonoids in moderate to excellent yields (66–98%). Unlike the aforementioned series, which yielded isoflavonoids in three steps, we still needed to demethylate our products. We attempted this with $AlCl_3$,[14] BCl_3,[15] and TMSI,[16] but as with our synthesis of daidzein only HI refluxed for 4 h proved successful (**Step 4**). This ultimately afforded us the series of 4-hydroxyisoflavonoids (**5**–**8**).

Using the same methodology as described above we set out to complete the synthesis of our library (**9**–**16**). We were successful in synthesizing 5-hydroxyisoflavonoids (**9**–**12**), however we had no luck utilizing the outlined scheme for 6-hydroxyisoflavonoids (**13**–**16**). This was unsuccessful in the first step of our pathway; that is, the formation of the enamine and protection of the hydroxyl. We attempted this in molar ratios of 1:1 up to 50:1 of acetophenone to DMF-DMA. In addition, we explored different temperatures and reaction times. Our best result yielded only 10% of crude product. We therefore explored initial protection of 6-hydroxyl. Although we were able to selectively protect one of the hydroxyls of 2,6-dihydroxyacetophenone simply by manipulation of reagent ratios with silyl protecting groups and benzyl; in both cases the subsequent enamine formation was unsuccessful. Ultimately, as with genistein, we found success with MOM-protection. Therefore, after the initial MOM-protection with chloromethyl methyl ether and *N,N*-diisopropylethylamine in CH_2Cl_2 (**Step pre-1**), we obtained the protected acetophenone, which we used without additional purification to obtain the enamine (**Step 1**). This went further through a ring closure/iodination reaction (**Step 2**) followed but the Suzuki cross-coupling (**Step 3**). Simple refluxing in concentrated HCl for one hour afforded the desired 6-hydroxyisoflavonoids (**13**–**16**) in moderate to good yields (**Step 4**).

In conclusion, we have presented a three- to five-step synthetic route to a host of isoflavonoid derivatives. The key synthetic steps involve enamine formation (**Step 1**), ring closure/iodination (**Step 2**), and Suzuki cross-coupling (**Step 3**). Additional steps beyond these are either deprotection (**Step 4**) or protection/deprotection (**Step pre-1/Step 4**).

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References and notes

1. Masuoka, N.; Isobe, T.; Kubo, I. *Phytother. Res.* **2006**, *20*, 206.
2. Baber, R. J. In *Isoflavones: Chemistry, Analysis, Function and Effect*; Preedy, V. R., Ed.; RSC Publishing, 2013; pp 3–13.
3. Tumova, L. *Čes. Slov. Farm.* **1995**, *44*, 18.
4. Malvy, D.; Galan, P.; Hercberg, S. *Cah. Nutr. Diet.* **2000**, *35*, 156.
5. Durgo, K.; Vukovic, L.; Rusak, G.; Osmak, M.; Colic, J. F. *Food Technol. Biotech.* **2007**, *45*, 69.
6. Hodgson, J. M.; Croft, K. D. *J. Sci. Food Agric.* **2006**, *86*, 2492.
7. Soidinsalo, O.; Wähälä, K. *J. Labelled Compd. Radiopharm.* **2006**, *49*, 973.
8. Whalley, J. L.; Bond, T. J.; Botting, N. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2569.
9. Biegasiewicz, K. F.; St. Denis, J. D.; Carroll, V. M.; Priefer, R. *Tetrahedron Lett.* **2010**, *51*, 4408.
10. Carroll, V. M.; St. Denis, J. D.; Biegasiewicz, K. F.; Priefer, R. In *Isoflavones: Chemistry, Analysis, Function and Effect*; Preedy, V. R., Ed.; RSC Publishing, 2013; pp 61–82.
11. St. Denis, J. D.; Gordon, J. S., IV; Carroll, V. M.; Priefer, R. *Synthesis* **2010**, 1590.
12. Belov, P.; Campanella, V. L.; Smith, A. W.; Priefer, R. *Tetrahedron Lett.* **2011**, *52*, 2276.
13. Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122.
14. Faria, T.; Silva, L.; Filho, J.; Chiari, E.; Oliveira, A. B. *J. Braz. Chem. Soc.* **2005**, *16*, 1415.
15. Al-Maharik, N.; Botting, N. *Tetrahedron* **2004**, *60*, 1637.
16. Jung, M.; Lyster, M. *J. Org. Chem.* **1977**, *42*, 3761.