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An efficient synthesis of daidzein, dimethyldaidzein, and isoformononetin

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ABSTRACT

Synthesis of the soy isoflavone, daidzein, and its derivatives, isoformononetin and dimethyldaidzein, through utilization of a novel synthetic pathway is reported. This synthesis employs an enamine addition and O-methylation of 2,4-dihydroxyacetophenone, a subsequent ring closure and iodination, followed by a Suzuki coupling with PEG 10000. Demethylation of either isoformononetin or dimethyldaidzein afforded daidzein.

1. Introduction

Flavonoids are a class of natural products that are composed of a three ring backbone, two of which are aryl moieties. They are a key contributor in a series of plant defense mechanisms acting as free-radical scavengers throughout the body.[1] The flavonoids encompass six subclasses including the flavones, flavonols, flavanones, isoflavones, anthocyanidins, and catechins.[2] One flavonoid subclass that has received a great deal of attention over the last decade for potential biological and medicinal applications is the isoflavones.

Soy isoflavones are found in the legume family of plants and typically exist in a 7-O-glycosylated state until being metabolized into aglycones.[3] Some of the most popular isoflavones include glycitein, genistein, formononetin, biochanin A (Fig. 1), and daidzein, **1** (Fig. 2). Of these, the most extensive studies have been focused on genistein and daidzein.[4]

Daidzein has gained particular interest in recent years for its biological applications. It functions much like genistein, in terms of its strong antioxidant activity and its estrogen-like structure allowing for altered growth, development, and function of estrogen-dependant target tissues,[5] but in addition, daidzein also has its own unique capabilities. It has been shown to elevate the activity of catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase in the skin and small intestine,[5] and inhibit osteoporosis in ovariectomized mice.[6] In addition, at low concentrations daidzein has demonstrated its ability to stimulate catecholamine synthesis through estrogen receptors,[7] and inhibit CYP1A1 in mouse hepatoma cell cultures showing a reduction in carcinogenesis.[8] Finally, it has been shown to be a potential treatment for neurodegeneration,[9] and has been proven to be more efficient than genistein in preventing ovariectomy-induced osteoporosis in rats.[10]

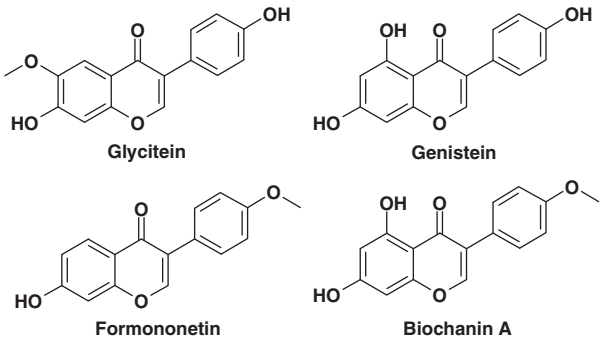

Figure 1. Common isoflavones found in soybeans.

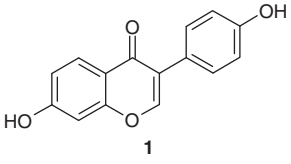

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Figure 2. Structure of daidzein.

Multiple syntheses have been carried out to produce daidzein. It has been recently prepared by initially producing 4-benzyloxysalicylaldehyde from resorcinol. A Wittig reaction, O-alkylation, an additional Wittig, RCM with Grubb's catalyst, subsequent hydroboration–oxidation to create the chromen ring, treatment with DDQ in an oxidation–dehydration reaction, and finally debenzylation and demethylation with $AlCl_3$/EtSH gave daidzein.[11] Other procedures have also been employed including utilization of resorcinol, 4-hydroxyphenylacetic acid, and BF_3-Et_2O to form a phenyl–benzyl ketone and subsequently to form daidzein in a reaction with Me-SO_2Cl, BF_3-Et_2O, and DMF.[12] It has also been demonstrated that

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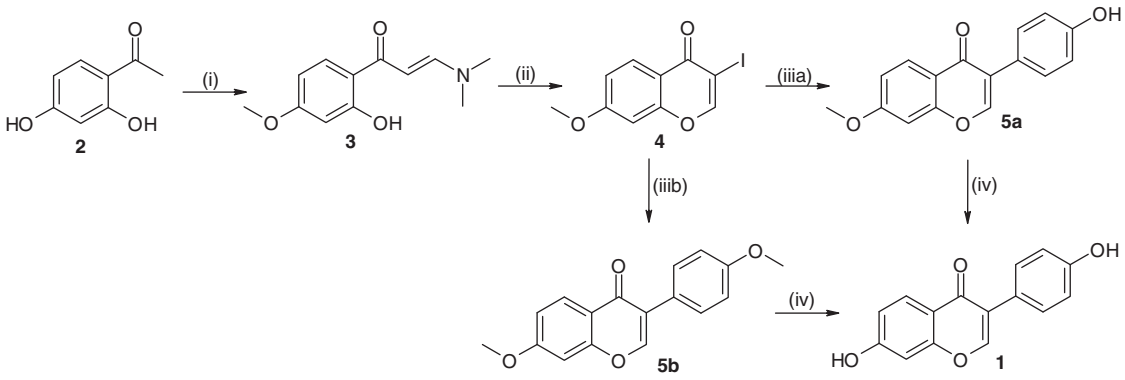

Scheme 1. Synthetic path to the isoflavones, isoformononetin, dimethyldaidzein, and daidzein. Reagents and conditions: (i) DMF-DMA, DMF, 80 °C, 24 h; (ii) I_2, MeOH, rt, 24 h; (iiia) 4-OH-PBA, Na_2CO_3, $Pd(OAc)_2$, PEG 10000, 50 °C, MeOH, 3 h; (iiib) 4-OMe-PBA, Na_2CO_3, $Pd(OAc)_2$, PEG 10000, 50 °C, MeOH, 3 h; (iv) HI, reflux, 4 h.

by using benzyl-protected acetophenones and running aldol condensation with 4-methoxybenzaldehyde, treatment with thallium nitrate for oxidative rearrangement, followed by addition of hydrochloric acid affords daidzein.[13]

Herein, we report an efficient, novel synthetic pathway to yield daidzein, as well as its derivatives, isoformononetin and dimethyldaidzein. This was accomplished through the utilization of an enamine addition and O-methylation, a ring closure and iodination, a Suzuki coupling with PEG 10000, and O-demethylation to afford our desired product, daidzein.

It has been demonstrated by Stevens and co-workers that *N,N*-dimethylformamide dimethylacetal (DMF-DMA) can be used with acetophenone derivatives to yield enamino-ketones.[14] Our synthesis (Scheme 1) began with commercially available 2,4-dihydroxyacetophenone (**2**) and DMF-DMA. Our original intention was strictly to add the enamine moiety to the starting acetophenone, but upon stirring at 80 °C in DMF for 24 h, we found that it went through an additional O-methylation on the 4-OH group, resulting in 3-dimethylamino-1-(2-hydroxy-4-methoxy)-phenylpropenone (**3**) in a respectable yield of 89%.[15] It has also been demonstrated that DMF-DMA is capable of O-methylation of phenols.[16] We made multiple attempts to isolate the non-O-methylated enamine product by performing the reaction with 1:1, 1:2, and 1:3 ratios of **2**:DMF-DMA as well as at various temperatures. Only the 1:2 ratio at 80 °C was determined mildly successful but still afforded >60% of **3**. Attempted isolation of the desired non-O-methylated product was very difficult due to its insolubility in ethyl acetate, chloroform, dichloromethane, and hexanes. The compound was finally determined to be soluble in acetonitrile and attempted recrystallization yielded very little product. As a result, we continued the synthesis conscious of the final O-demethylation step.

As did Stevens et al.,[14] our synthesis continued with a ring closure and iodination of our enamine added product, **3**. Methylation of the 4-OH group in the first step did not hinder a successful ring closure and iodination of our enamine added product, 7-methoxy-3-iodo-4*H*-chromen-4-one (**4**) in an 81% yield.[17] This was followed by a Suzuki coupling to afford daidzein derivatives, isoformononetin (**5a**) or dimethyldaidzein (**5b**) when using the respective phenylboronic acid (PBA) derivatives.[14] A typical Suzuki coupling involves the use of a phosphine-based ligand which can be toxic, expensive, and difficult to separate from the reaction mixture.[18] Liu et al. have recently demonstrated a green approach to this reaction. The use of poly(ethylene glycol) 4000 (PEG 4000) as the ligand, along with $Pd(OAc)_2$, Na_2CO_3, in H_2O or MeOH effectively gave the desired Suzuki products.[19] In lieu of PEG 4000, we employed PEG 10000,[20] which did indeed afford isoformononetin (7-methoxy-3-(4-hydroxyphenyl)-4*H*-chromen-4-one) (**5a**, 98%) and dimethyldaidzein (7-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one) (**5b**, 90%).[21] The PEG/$Pd(OAc)_2$ could also be reused without the further addition of palladium.

Our final step required the demethylation of **5a** and **5b** to yield our desired product, daidzein, **1**. A series of demethylation techniques utilizing BBr_3, BCl_3,[22] $AlCl_3$,[23] and trimethylsilyl iodide (TMSI)[24] were initially attempted on both derivatives. The only method that was mildly effective was the use of TMSI because of its ability to demethylate the 4′-OMe on the dimethyldaidzein derivative after one week at reflux in chloroform solvent. The method that proved effective for both derivatives involved dissolving the respective daidzein derivative in HI and maintaining it at reflux for 4 h.[25] Once the product was collected and subjected to silica gel chromatography, we obtained our desired product, daidzein, in high yields (isoformononetin—89%, dimethyldaidzein—94%).[26]

In conclusion, a novel pathway has been demonstrated for the synthesis of daidzein, through either isoformononetin or dimethyldaidzein in four steps, with an overall yield of 62% and 61%, respectively.

Acknowledgments

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References and notes

1. Li, M.; Han, X.; Yu, B. *J. Org. Chem.* **2003**, *68*, 6842.
2. Song, J.; Kwon, O.; Chen, S.; Daruwala, R.; Eck, P.; Park, J. B.; Levine, M. *J. Biol. Chem.* **2002**, *277*, 15252.
3. Phillips, D.; Kapulnik, Y. *Trends Microbiol.* **1995**, *3*, 58.
4. Chen, J.; Wang, S. *Drug Metab. Dispos.* **2005**, *33*, 1777.
5. Liu, H.; Zhang, C.; Zeng, W. *Domest. Anim. Endocrinol.* **2005**, *31*, 258.
6. Fujioka, M.; Uehara, M.; Wu, J.; Adlercreutz, H.; Suzuki, K.; Kanazawa, K.; Takeda, K.; Yamada, K.; Ishimi, Y. *J. Nutr.* **2004**, *134*, 2623.
7. Liu, M.; Yanagihara, N.; Toyohira, Y.; Tsutsui, M.; Ueno, S.; Shinohara, Y. *Endocrinology* **2007**, *148*, 5348.
8. Shertzer, H.; Puga, A.; Chang, C.; Smith, P.; Nebert, D. W.; Setchell, D. R.; Dalton, T. P. *Chem. Biol. Interact.* **1999**, *123*, 31.
9. Mao, Z.; Zheng, Y.; Zhang, Y.; Han, B.; Zhu, X.; Chang, Q.; Hu, X. *Molecules* **2007**, *12*, 1455.
10. Picherit, C.; Coxam, V.; Bennetau-Pelissero, C.; Kati-Coulibaly, S.; Davicco, M.; Lebecque, P.; Barlet, J. *J. Nutr.* **2000**, *130*, 1675.
11. Li, S.; Chen, P.; Chen, L. *Tetrahedron Lett.* **2009**, *50*, 2121.
12. Yeap, G.; Yam, W.; Ito, M. *Liq. Crystallogr.* **2007**, *34*, 649.
13. Dung, S.; Cho, S.; Dang, T. *Eur. J. Med. Chem.* **2003**, *38*, 537.
14. Vasselin, D.; Westwell, A.; Matthews, C.; Bradshaw, T. D.; Stevens, M. F. G. *J. Med. Chem.* **2006**, *49*, 3973.
15. *Synthesis of 3-dimethylamino-1-(2-hydroxy-4-methoxy)-phenylpropenone* (**3**): 2,4-Dihydroxyacetophenone (**2**, 3.00 g, 0.0197 mol) was dissolved into DMF (150 mL) and warmed to 74 °C in an oil bath. Subsequently, DMF-DMA (9.67 g, 0.0812 mol) was added to the flask dropwise. The resulting mixture was stirred for 24 h then cooled to room temperature. After quenching with water

(200 mL), extracting with Et_2O (5 × 120 mL), washing with H_2O (100 mL), drying with $MgSO_4$, and concentrating under reduced pressure, afforded a dark green solid. The resulting solid was subjected to silica gel chromatography (ethyl acetate) yielding, 3-dimethylamino-1-(2-hydroxy-4-methoxy)-phenylpropenone (**3**: 3.87 g, 0.0175 mol, 89%), as a bright green solid.
R_f = 0.74 (EtOAc).
Mp = 130–133 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (d, 1H, *J* = 12.0 Hz, C*H*═CH), 7.61 (d, 1H, *J* = 9.2 Hz, Ar-*H*), 6.41 (d, 1H, *J* = 2.4 Hz, Ar-*H*), 6.38 (dd, 1H, *J* = 2.4, 9.2 Hz, Ar-*H*), 5.68 (d, 1H, *J* = 12.0 Hz, CH═C*H*), 3.82 (s, 3H, –OCH_3), 3.18 (s, 3H, –NCH_3), 2.96 (s, 3H, –NCH_3).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.6, 165.5, 164.3, 154.0, 129.7, 113.8, 106.4, 101.0, 89.8, 55.4, 45.4, 37.4.
HR-MS (ESI) calculated for (M+H$^+$): 222.1125, found: 222.11183.

16. Sinkevich, Y.; Shchekotikhin, A.; Luzikov, Y. *Chem. Heterocycl. Compd.* **2007**, *43*, 1252.
17. *Synthesis of methoxy-3-iodo-4H-chromen-4-one* (**4**): A reaction flask was charged with 3-dimethylamino-1-(2-hydroxy-4-methoxy)-phenylpropenone (**3**: 0.930 g, 0.00420 mol), iodine (1.611 g, 0.00635 mol), and methanol (110 mL) and stirred at room temperature for 24 h. Methanol was removed to yield a red-black residue that was treated with satd Na_2SO_3 to remove latent iodine until the mixture was clear. The mixture was extracted with $CHCl_3$ (3 × 50 mL), dried with $MgSO_4$, and concentrated under reduced pressure to give an off-white solid, which was subjected to silica gel chromatography (3:1 hexanes/EtOAc) yielding 7-methoxy-3-iodo-4*H*-chromen-4-one (**4**: 1.192 g, 0.00392 mol, 81%) as a white solid.
R_f = 0.54 (3:1 hexanes/EtOAc).
Mp = 161–164 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (s, 1H, olefinic *H*), 8.15 (d, 1H, *J* = 8.8 Hz, Ar-*H*), 7.00 (dd, 1H, *J* = 2.4, 8.8 Hz, Ar-*H*), 6.84 (d, 1H, *J* = 2.4 Hz, Ar-*H*), 3.91 (s, 3H, OCH_3).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 164.3, 157.9, 157.2, 128.1, 115.7, 115.3, 100.0, 87.1, 55.9.
HR-MS (ESI) calculated for (M+H$^+$): 302.9513, found: 302.95090.

18. Ren, L.; Meng, L. *Express Poly. Lett.* **2008**, *2*, 251.
19. Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122.
20. St. Denis, J. D.; Gordon, J. S., IV; Carroll, V. M.; Priefer, R. *Synthesis* **2010**, 1590.
21. *General procedure for Suzuki coupling*: A round bottom flask was charged with methanol (8.60 g) and Na_2CO_3 (0.354 g, 0.00285 mol) and allowed to stir. PEG 10000 (9.95 g) was ground to fine consistency and added to the flask with $Pd(OAc)_2$ (0.0326 g, 0.0001 mol). The reaction mixture with attached condenser was then warmed to 50 °C in a water bath. Once the mixture turned black, 7-methoxy-3-iodo-4*H*-chromen-4-one (**4**: 0.402 g, 0.00132 mol) and 4-hydroxyphenylboronic acid (0.275 g, 0.00200 mol) were added and left to stir for 3 h. Et_2O (100 mL) was added, and the resulting mixture was emptied into a Büchner funnel, and an additional aliquot of Et_2O (200 mL) was run through the solid. The ethereal extract was concentrated under reduced pressure to yield an off-white solid which was subjected to silica gel chromatography (3:1 hexanes/EtOAc) yielding 7-methoxy-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (**5a**: 0.347 g, 0.00129 mol, 98%), as a white solid.
R_f = 0.43 (3:1 hexanes/EtOAc).
Mp = 198–201 °C.
^{1}H NMR (400 MHz, DMSO) δ = 9.55 (s, 1H, –O*H*), 8.38 (1H, olefinic *H*), 8.03 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 7.40 (d, 2H, *J* = 8.8 Hz, phenyl-*H*), 7.16 (d, 1H, *J* = 2.4 Hz, Ar-*H*), 7.08 (dd, 1H, *J* = 2.4, 8.4 Hz, Ar-*H*), 6.81 (d, 2H, *J* = 8.8 Hz, phenyl-*H*), 3.91 (s, 3H, –OCH_3).
^{13}C NMR (100 MHz, DMSO) δ = 174.7, 163.7, 157.5, 157.3, 153.2, 130.1, 127.0, 123.7, 122.3, 117.6, 115.0, 114.8, 100.6, 56.1.
HR-MS (ESI) calculated for (M+H$^+$): 269.0808, found: 269.08115.
Compound **5b**: (0.264 g, 0.000934 mol, 90%), as a white solid.
R_f = 0.66 (3:1 hexanes/ethyl acetate).
Mp = 138–141 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (d, 1H, *J* = 8.8 Hz, Ar-*H*), 7.93 (s, 1H, olefinic *H*), 7.51 (d, 2H, *J* = 8.0 Hz, phenyl-*H*), 7.00 (dd, 1H, *J* = 1.2, 8.8 Hz, Ar-*H*), 6.98 (d, 2H, *J* = 8.0 Hz, phenyl-*H*), 6.86 (d, 1H, *J* = 1.2 Hz, Ar-*H*), 3.92 (s, 3H, –OCH_3), 3.85 (s, 3H, –OCH_3).
^{13}C NMR (400 MHz, $CDCl_3$) δ = 175.9, 163.9, 159.5, 157.9, 152.0, 130.1, 127.8, 124.9, 124.2, 118.4, 114.5, 113. 9, 100.1, 55.8, 55.3.
HR-MS (ESI) calculated for (M+H$^+$): 283.0965, found: 283.09656.

22. Al-Maharik, N.; Botting, N. *Tetrahedron* **2004**, *60*, 1637.
23. Faria, T.; Silva, L.; Filho, J.; Chiari, E.; Oliveira, A. B. *J. Braz. Chem. Soc.* **2005**, *16*, 1415.
24. Jung, M.; Lyster, M. *J. Org. Chem.* **1977**, *42*, 3761.
25. Shriner, R. L.; Hull, C. J. *J. Chem. Soc.* **1945**, 228.
26. *General procedure for demethylation*: A reaction flask was charged with 7-methoxy-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (**5a**, 0.125 g, 0.000462 mol) and HI (5 mL) and held at reflux for 4 h. Upon cooling, 30% KOH (3 mL) was added and the resulting mixture was stirred for an additional 15 min. Subsequently, concd HCl (3 mL) was added forming a precipitate. The resulting mixture was vacuum filtered and a red-brown solid was collected. The solid was subjected to silica gel chromatography (3:2 EtOAc/hexanes) affording daidzein (**1**, 0.105 g, 0.000410 mol, 89%) as a white solid.
R_f = 0.57 (3:2 EtOAc/hexanes).
Mp = 315–318 °C.
^{1}H NMR (400 MHz, DMSO) δ = 10.90 (s, 1H, –O*H*), 9.63 (s, 1H, –O*H*), 8.34 (s, 1H, olefinic *H*), 8.00 (d, 1H, *J* = 8.8 Hz, Ar-*H*), 7.41 (d, 2H, *J* = 8.4 Hz, phenyl-*H*), 6.97 (dd, 1H, *J* = 2.0, 8.8 Hz, Ar-*H*), 6.90 (d, 1H, *J* = 2.0 Hz, Ar-*H*), 6.84 (d, 2H, *J* = 8.4 Hz, phenyl-*H*).
^{13}C NMR (100 MHz, DMSO) δ = 175.7, 163.5, 158.4, 158.1, 153.8, 131.1, 128.3, 124.4, 123.5, 117.6, 116.1, 115.9, 103.1.
HR-MS (ESI) calculated for (M+H$^+$): 255.0652, found: 255.06479.