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BF_3OEt_2 and $MeSO_3H$-Promoted reactions of phenols and ethyl phenylpropiolate as a synthetic routes to neoflavones and a potential route to flavones

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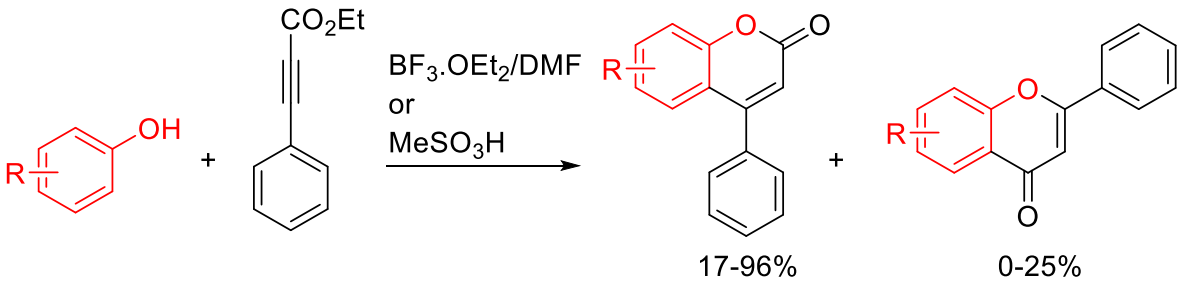
Abstract

The $BF_3.OEt_2$ and $MeSO_3H$-promoted reactions of phenols and ethyl phenylpropiolate to give neoflavones in 17-96% and flavones in 0-25% yield are described. In general, phenols with activating substituents favor the formation of neoflavones under both $BF_3.OEt_2$ and $MeSO_3H$-promoted reaction conditions. Phenol and *p*-Chlorophenol reacted with ethyl phenylpropiolate under the $MeSO_3H$-promoted reaction conditions to give close to 1:1 mixtures of the corresponding neoflavones and flavones.

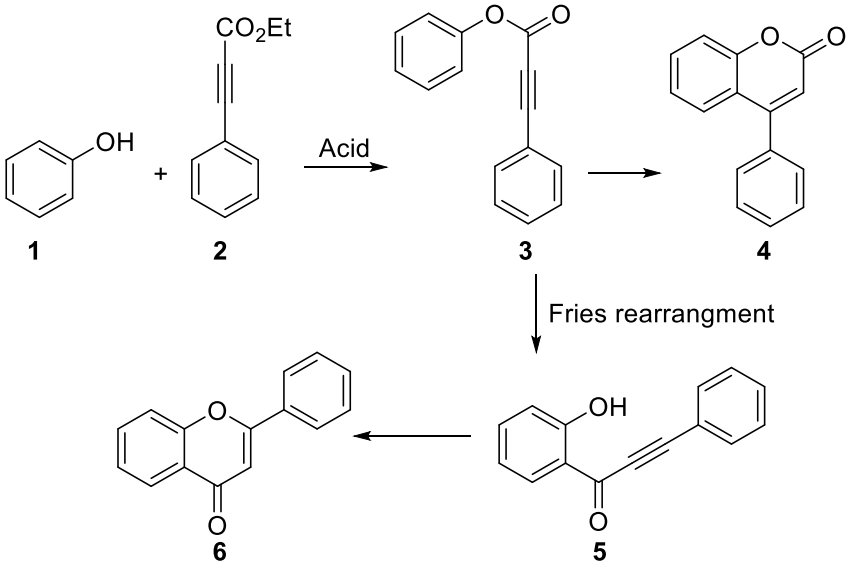


Keywords: Flavones, neoflavones, phenols, ethyl phenylpropiolate, Fries rearrangement, Michael reaction

Introduction

A significant number of flavonoids have been isolated and characterized at the Department of Chemistry, University of Botswana.[1-4] As part of a broader research project of drug discovery, the isolated compounds are supposed to be developed as lead compounds. However, the compounds are mostly isolated in minute quantities from medicinal plants and that has proved to be the bottleneck for the development of the compounds into lead compounds for the drug discovery.

Synthesis provides a possible route for accessing flavonoids in quantities that will allow their development into lead compounds for drug discovery. Our research group therefore initiated a research project on development of methods for the synthesis of flavonoids. A number of these methods have been reported in literature.[5, 6] Here, we report the acid-promoted reactions of phenols and ethyl phenylpropiolate as a possible synthetic route to neoflavones or/and flavones. The theoretical basis of using the acid-mediated reaction of phenols and ethyl phenylpropiolate is summarized in scheme 1. It was anticipated that the synthetic process will proceed through a *trans*-esterification reaction of phenol **1** and propiolate **2** to give ester **3** which will in turn undergo an intramolecular electrophile aromatic substitution-Michael addition ring closure reaction to give coumarin **4**. Alternatively, ester **3** will undergo a Fries rearrangement reaction to give intermediate **5** which can in turn undergo a ring closing Michael type reaction to give flavone **6**. It is important to note that literature reports on the Lewis acid-promoted reactions of phenols and ethyl phenylpropiolate have reported neoflavones as the only products.[7-9]

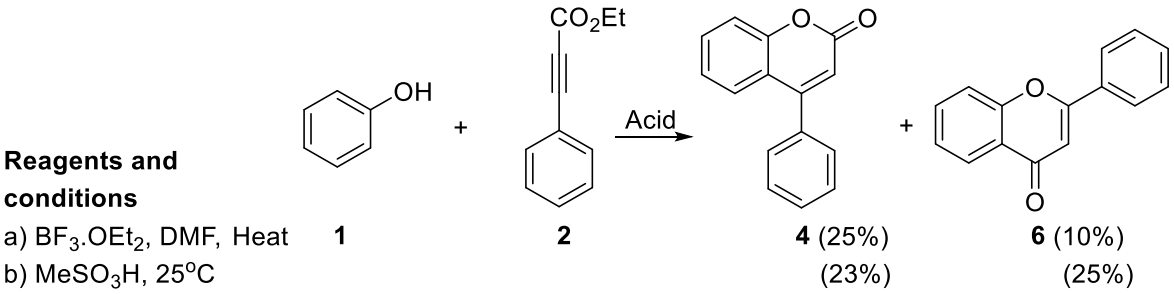


Scheme 1. Acid-mediated reaction of Phenols and ethyl phenylpropiolate.

Results and Discussion

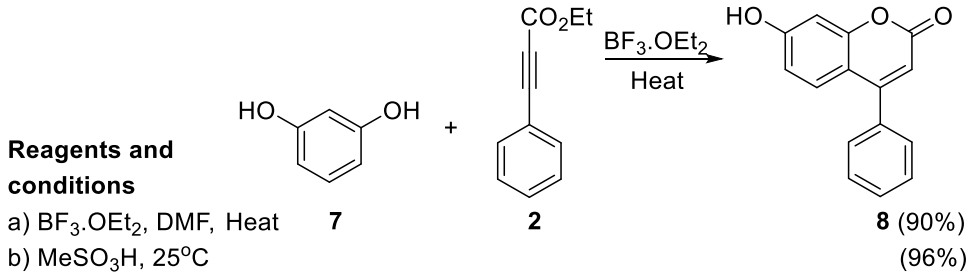
The model reaction of this study involved heating a mixture of phenol **1** and ethyl phenylpropiolate **2** in the presence of $BF_3.OEt_2$, Scheme 2. After 18 hours of heating, the reaction was quenched with distilled water and the organic components were extracted with chloroform. Purification of the organic extract using column chromatography gave neoflavone **4** in 15% yield together and flavone **6** in 5% yield. Addition of controlled

amounts of DMF to the reaction mixture increased the yield of neoflavone **4** to 25% and that of the flavone **6** to 10% yield and reduced the reaction time to 3 hours. In a parallel reaction, a mixture of phenol **1**, propiolate **2** and $MeSO_3H$ was stirred at room temperature for 2 hours to give neoflavone **4** in 23% yield and flavone **6** in 25% yield.



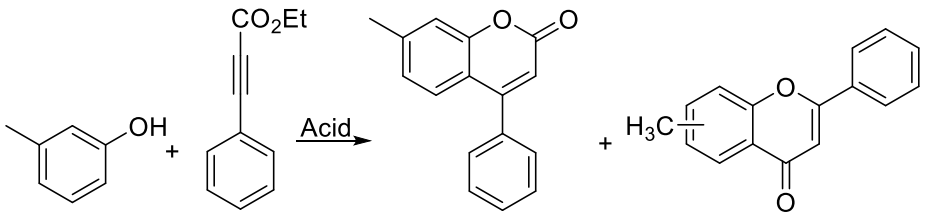
Scheme 2. Acid-mediated reaction of phenol **1** and propiolate **2.**

Encouraged by the results discussed above, we set out to investigate the effects of substituted phenols on the reaction. Interestingly, subjection of a mixture of resorcinol **7** and propiolate **2** to reaction conditions a) gave only neoflavone **8** in excellent yields of 90%, Scheme 3. The corresponding flavone was not detected. The reaction of **2** and **7** in the presence of $MeSO_3H$ also gave only neoflavone **8** in 96%.



Scheme 3. Acid-mediated reaction of resorcinol **7** and propiolate **2.**

The observation that the additional hydroxyl group of resorcinol **7** completely shuts down the Fries rearrangement and consequently the formation of the corresponding flavone was a striking aspect of the acid-mediated reaction of phenols with propiolate **2**. It was reasoned that groups that donate electrons to phenol less than the hydroxyl group will not stop the Fries rearrangement. Indeed, when a mixture of *m*-cresol **9**, propiolate **2** and excess $BF_3.OEt_2$ in the presence of controlled amount of DMF was heated, neoflavone **10**, flavones **11** and **12** were isolated in 20%, 4% and 6% respectively, Scheme 4, reagent and conditions a). On the other hand, exposure of a mixture of *m*-cresol **9** and propiolate **2** to the action of $MeSO_3H$ led to the formation of neoflavone **10** in 80% and flavone **11** in 15%, Scheme 4, reagents and conditions b). Flavone **12** was not detected under reaction conditions b).



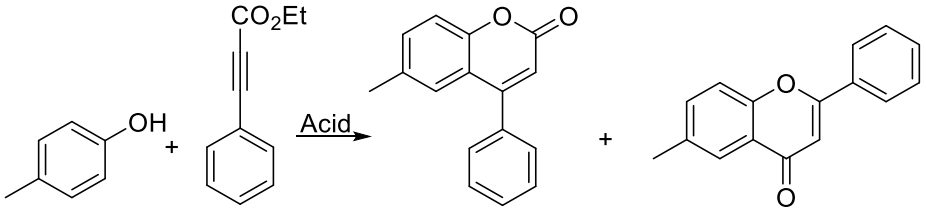
Reagents & conditions

a) $BF_3.OEt_2$, DMF, Heat **9** **2** **10** (20%) **11** (7-CH_3, 4%) **12** (5-CH_3, 6%)

b) $MeSO_3H$, 25°C (80%) **11** (7-CH_3,15%)

Scheme 4. Acid-mediated reaction of *m*-cresol and propiolate **2.**

p-Cresol participated in the $BF_3.OEt_2$-mediated reaction with propiolate **2** to give neoflavone **14** in 35% yield and flavone **15** in 15%, Scheme 5, reagents and conditions a). The $MeSO_3H$-promoted reaction of *p*-cresol **13** and propiolate **2** gave neoflavone **14** in 42% and flavone **15** in 12% yield scheme 5, reagents and conditions b). The low yield of this reaction can be attributed to non-cooperative directing effects of the methyl and hydroxyl groups of *p*-cresol **13**.



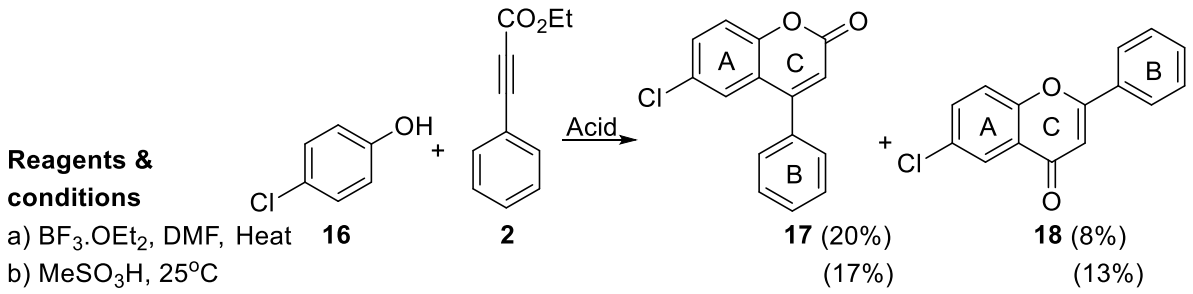
Reagents & conditions

a) $BF_3.OEt_2$, DMF, Heat **13** **2** **14** (35%) **15** (15%)

b) $MeSO_3H$, 25°C (42%) (12%)

Scheme 5. Acid-mediated reaction of *p*-cresol and propiolate **2.**

It was anticipated that deactivating groups on the phenol would stop both the Michael reaction which led to the formation of the neoflavone and the Fries rearrangement which gave the flavone. Indeed, when a mixture of 4-nitrophenol and propiolate **2** was subjected to either reaction conditions a) or b), none of the corresponding products were detected. However, *p*-chlorophenol **16** reacted with propiolate **2** under reaction conditions a) to give neoflavone **17** in 20% yields and flavone **18** in 8%. Under reaction conditions b) the reaction proceeded to give neoflavone **17** in 17% yield and flavone **18** in significantly increased yield of 13%. The increase in the proportion of flavone **18** when the reaction of **16** and **2** is performed under reaction conditions b) has potential for optimization to be a reliable route to flavones with amenable electron withdrawing groups on ring A.



Scheme 6. Acid-promoted reaction of *m*-cresol **16** and propiolate **2.**

Conclusions

In conclusion, the acid-promoted reaction of phenols and ethyl phenylpropiolate was described as a route to neoflavones and a potential route to flavones. Participation of phenols with activating substituents in the reaction were in general found to favour the formation of neoflavones while phenols and p-chlorophenol gave close to 1:1 ratio of the corresponding neoflavones and flavones.

Experimental Section

Typical procedure for $BF_3.OEt_2$-promoted reaction of phenols and ethyl phenylpropiolate

A mixture of phenol **1** (0.50 g, 5.3 mmol) with ethyl phenylpropiolate **2** (0.93 g, 5.3 mmol) in the presence of excess $BF_3.OEt_2$ (3 mL, 24.3 mmol) and DMF (1.88 mL, 24.3 mmol) was refluxed for 3 h. The reaction was quenched with water and extracted with chloroform. The extract was concentrated using rotavapor and adsorbed on silica before been subjected to column chromatography and eluted with *n*-hexane-ethyl acetate (8: 3)

Typical procedures for $MeSO_3H$-promoted reaction of phenols and ethyl phenylpropiolate

A mixture of phenol **1** (0.5 g, 5.3 mmol) and ethyl phenylpropiolate **2** (0.93 g, 5.3 mmol) in the presence of excess methanesulfonic acid (3 mL, 46.2 mmol) was stirred at room temperature for 2 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with chloroform. The extract was then concentrated using rotavapor and subjected to column chromatography eluting with *n*-hexane-ethyl acetate (8:3).

Physiochemical and spectral data of the synthesized compounds

4-Phenyl-2*H*-chromen-2-one (**4**)**.**[10] Yellow solid, mp 96-98 °C (Lit. 97-98 °C);[10] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (1H, s, H-3), 7.21 (1H, dd J = 7.6 Hz, H-6), 7.36 (1H, d J = 8.3 Hz, H-8), 7.48 (7H, m, H-2', 3', 4', 5, 5', 6' and 7); ^{13}C NMR (126 MHz, $CDCl_3$) δ 115.3 (C-3), 117.3 (C-8), 119.1 (C-4a), 124.2 (C-6), 127.1 (C-5), 128.5 (C-2'), 128.6 (C-6'), 128.9 (C-3', 129.0 (C-5'), 129.7 (C-7), 132.0 (C-4') 135.3 (C-1'), 154.3 (C-8a), 155.7 (C-4), 160.7 (C-2); GC-MS (EI) *m/z* 222 $[M]^+$

2-Phenyl-4*H*-chromen-4-one (6).[11] White solid, mp 99-101 °C (Lit. 100-102 °C);[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (1H, s, H-3), 7.43 (1H, dd J = 7.5 Hz, H-4'), 7.54 (3H, m, H-3', 5' and 6), 7.58 (1H, d J = 8.5 Hz, H-8), 7.71 (1H, dd, J= 7.8 Hz, H-7), 7.94 (2H, m, H-2' and 6'), 8.25 (1H, d J = 7.9 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ

107.6 (C-3), 118.1 (C-8), 124.0 (C-4a), 124.0 (C-6), 125.2 (C-5), 125.8 (C-4'), 126.4 (C-2' and C-6'), 128.8 (C-3'), 129.0 (C-5'), 131.6 (C-7), 131.9 (C-1'), 133.8 (C-), 156.3 (C-8a), 163,5 (C-2), 178.4 (C-4); GC-MS (EI) *m/z* 222 $[M]^+$

7-Hydroxy-4-phenyl-2*H*-chromen-2-one (8).[12] Yellow solid, mp 249-251 °C (Lit.248-252 °C);[12] ^{1}H NMR (500 MHz, Acetone) δ 6.10 (1H, s, H-8), 6.83 (2H, m, H-3 and 6), 7.33 (1H, d J = 8.5 Hz, H-5), 7.53 (2H, m, H-2' and 6'), 5.57 (3H, m, H-3', 4'and 5'), 9.49 (1H, s, OH); ^{13}C NMR (126 MHz, Acetone) δ 103.6 (C-8), 111.9 (C-6), 112.3 (C-4a), 113.7 (C-3), 129.2 (C-5), 129.3 (C-2' and 6'), 129.7 (C-3' and 5'), 130.4 (C-1'), 156.6 (C-4), 157.1 (C-8a), 160.9 (C-7), 162.2 (C-2); GC-MS (EI) *m/z* 238 $[M]^+$

7-Methyl-4-phenyl-2*H*-chromen-2-one (10).[10] Yellow paste; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (3H, s, -CH_3), 6.31 (1H, s, H-3), 7.04 (1H, d J = 8.2 Hz, H-6), 7.22 (1H, s, H-8), 7.37 (1H, d J = 8.2 Hz, H-5), 7.54 (2H, m, H-2' and 6'), 7.52 (3H, m, H-3', 4' and 5'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (-$\underline{C}H_3$), 113.0 (C-3), 115.6 (4a), 116.5 (C-8), 124.3 (C-6), 125.7 (C-5), 127.4 (C-2' and C-6'), 127.8 (C-3' and 5'), 128.6 (C-4'), 134.4 (C-1'), 142.2 (C-7), 153.3 (C-8a), 154.7 (C-4), 160.1 (C-2); GC-MS (EI) *m/z* 236 $[M]^+$

7-Methyl-2-phenyl-4*H*-chromen-4-one (11).[11] Yellow solid, mp 126-128 °C (lit. mp 122-124 °C).[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (3H, s, -C$\underline{H}_3$), 6.80 (1H, s, H-3), 7.23 (1H, d J = 8.1 Hz, H-6), 7.37 (1H, s, H-8), 7.52 (3H, m, H = 3', 4' and 5'), 7.91 (2H, m, H = 2' and 6'), 8.10 (1H, d, H = 8.1 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7 (-$\underline{C}H_3$), 107.4 (C-3), 117.7 (C-8), 121.5 (C-4a), 125.3 (C-6), 126.1 (C-3' and 5'), 126.6 (C-4'), 128.9 (C-2' and 6'), 131.4 (C-5), 131.8 (C-1'), 145.0 (C-7), 156.3 (8a), 163.0 (C-2), 178.3 (C-4); GC-MS (EI) *m/z* 236 $[M]^+$

5-Methyl-2-phenyl-4*H*-chromen-4-one (**12).**[11] White paste, ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (3H, s, -C$\underline{H}_3$), 6.76 (1H, s, H-3), 7.14 (1H, d J = 7.3 Hz, H-6), 7.40 (1H, d J = 7.3 Hz, H-8), 7.53 (3H, m, H-3', 4' and 5'), 7.92 (3H, m, H-2', 5 and 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.6 (-$\underline{C}H_3$), 108.7 (C-3), 116.0 (C-8), 122.2 (C-4a), 126.0 (C-2' and 6'), 127.6 (C-4'), 128.9 (C-3' and 5'), 131.3 (C-6), 131.5 (C-1'), 132.6 (C-7), 140.9 (C-5), 157.6 (8a), 161.6 (C-2), 180.5 (C-4); GC-MS (EI) *m/z* 236 $[M]^+$

6-Methyl-4-phenyl-2*H*-chromen-2-one (14).[12] Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (3H, s, -C$\underline{H}_3$), 6.34 (1H, s, H-3), 7.25 (1H, s, H-5), 7.29 (1H, d J = 8.4 Hz, H-8), 7.35 (1H, dd J = 8.4 and 2.1 Hz, H-7), 7.44 (2H, m, H-2' and 6'), 7.53 (3H, m, H-3', 4' and 5'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.9 (-$\underline{C}H_3$), 115.2 (C-3), 117.1 (C-8), 118.7 (C-4a), 126.7 (C-5), 128.4 (C-2', C-6'), 128.9 (C-3' and C-5'), 129.6 (C-4'), 132.9 (C-1'), 133.9 (C-7), 135.4 (C-6), 152.3 (C-8a), 155.6 (C-2), 161.0 (C-4); GC-MS (EI) *m/z* 236 $[M]^+$

6-Methyl-2-phenyl-4*H*-chromen-4-one (**15).**[11] White solid, mp 120-123 °C (Lit mp 122-123 °C);[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (3H, s, -C$\underline{H}_3$), 6.81 (1H, s, H-3), 7.51 (5H, m, H-3', 4', 5', 7 and 8), 7.92 (2H, m, H-2' and 6'), 8.02 (1H, s, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ δ 120.9 (-$\underline{C}H_3$), 107.5 (C-3), 117.9 (C-8), 123.6 (C-4a), 125.1 (C-5), 126.3 (C-2', C-6'), 129.0 (C-3' and C-5'), 131.5 (C-4'), 131.9 (C-1'), 135.0 (C-7), 135.2 (C-6), 154.6 (C-8a), 163.3 (C-2), 178.6 (C-4); GC-MS (EI) *m/z* 236 $[M]^+$

6-Chloro-4-phenyl-2*H*-chromen-2-one (**17).**[12] Yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (1H, s, H-3), 7.35 (1H, d J = 8.7 Hz, H-8), 7.44 (3H, m, H-2', 4' and 6'), 7.50 (1H, dd J = 8.8 and 2.5 Hz, H-7), 7.55 (3H, m, H-3', 5' and 7); ^{13}C NMR (126 MHz, $CDCl_3$) δ 116.2 (C-3), 118.8 (C-8), 120.2 (C-4a), 126.4 (C-5), 128.3 (C-2' and 6'), 129.1 (C-3' and 5'), 129.7 (C-6), 130.0 (C-4'), 131.9 (C-7), 134.6 (C-1'), 152.6 (C-8a), 154.6 (C-4), 160.0 (C-2). GC-MS (EI) *m/z* 257 $[M]^+$

6-Chloro-2-phenyl-4*H*-chromen-4-one (18).[11] White solid. mp 183-186 °C (Lit. mp 182-185 °C),[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (1H, s, H-3), 7.55 (4H, m, H-3', 4', 5' and 8), 7.65 (1H, dd J = 7.8 and 2.6 Hz, H-7), 7.92 (2H, dd J = 7.8 and 1.9 Hz, H-2' and 6'), 8.20 (1H, d J = 2.6 Hz, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 107.5 (C-3), 119.8 (C-8), 125.0 (C-4a), 125.2 (C-4'), 126.4 (C-2' and 6'), 129.1 (C-3' and 5'), 131.2 (C-6), 131.5 (C-1'), 131.9 (C-5), 134.0 (C-7), 154.6 (C-8a), 163.7 (C-2), 177.2 (C-4). GC-MS (EI) *m/z* 257 $[M]^+$

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Supplementary Material

NMR spectra of the prepared neoflavones and flavones can be found online in the supplementary material.

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