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A highly efficient and environmentally benign synthesis of 6,8-dibromoflavones, 8-bromoflavones, 5,7-dibromoaurones and 7-bromoaurones☆

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This work is dedicated to my teacher Professor K. Dey on the occasion of his 65th birthday

Abstract—Various ring substituted 6,8-dibromoflavones (**3a–e**) as well as 8-bromoflavones (**3f–j**) can be synthesized easily from the corresponding 2′-hydroxychalcones (**1a–j**) in good yields and in two steps under environmentally benign reaction conditions. This can be achieved by bromination with concomitant cyclization by using a combination of vanadium pentoxide, hydrogen peroxide and ammonium bromide in dichloromethane-water at 0–5 °C, followed by dehydrobromination of the brominated products **2a–j** using 0.2 M ethanolic KOH solution at ice-bath temperature. On the other hand, various 5,7-dibromoaurones and 7-bromoaurone derivatives **6a–c** can be obtained, exclusively, from the corresponding 2′-acetoxychalcones (**4a–c**) in good yields and in two steps by tuning the reaction conditions.

Aurones[1] [2-benzylidenebenzofuran-3(2*H*)-ones] and flavones[2] [2-phenylchromones] are structurally isomeric compounds, which are widely distributed in Nature. Among them, flavones are well known in the literature due to their wide range of biological activities,[3] such as anti-oxidant, anti-inflammatory, anti-viral,[4] anti-cancer[5] and chemo preventative activities.[6] Recently Medina et al. reported[7] that some flavonoids possess anxiolytic activity and low sedative or myorelaxant effects. They have also noted that some brominated flavones, particularly 6-bromoflavone and 6-bromo-3′-nitroflavone, showed activities close to or higher than that of diazepam. Some 8-bromoflavone derivatives, namely 8-bromo-5,7,4′-trimethoxyflavone (**3g**) might be useful synthetic precursors for the synthesis of biologically active natural products such as vitexin[8] and aciculatin.[9] The synthesis of compound **3g** was first reported by Wheeler and Hutchins[10] from the corresponding 2′-hydroxy-4,4′,6′-trimethoxychalcone by bromination using molecular bromine followed by cyclization under basic conditions. Later on, Chen and his group reported[11] the synthesis of compound **3g** in a sequence that used selenium dioxide oxidation. Later, Donnelly et al.[12] also synthesized **3g** along with 7-bromo-aurone derivative **6c** in the ratio 8:5 by cyclization of 2′-hydroxy-4,4′,6′-trimethoxychalcone dibromide using ethanolic KOH solution. They concluded that a substituent either at the 4′- or 6′-position on the A-ring did not favour the exclusive formation of the flavone. The synthesis of brominated flavones from 2′-hydroxychalcone can be accomplished using molecular bromine followed by cyclization with a base or from 2-hydroxy-4,6-dimethoxyacetophenone in three subsequent steps. Both procedures have drawbacks since both molecular bromine and selenium dioxide are harmful chemicals. At the same time, molecular bromine is difficult to handle and provides relatively low yields of the brominated products. Therefore, a methodology that is environmentally benign, clean, efficient and yet unambiguous is still required.

Taking a cue from the discovery of vanadium bromoperoxidase (VBrPO),[13] a vanadium enzyme, which catalyzes bromination of marine natural products as well as

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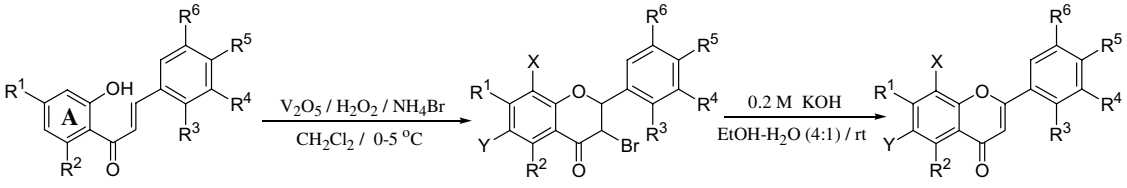
the earlier results reported by Clague and Butler[14] and others,[15] we have observed that vanadium pentoxide, hydrogen peroxide and tetrabutylammonium bromide are a good combination for generating reactive bromonium ions.[16] Moreover, the promoter (V_2O_5) and the oxidant (H_2O_2) are environmentally acceptable reagents. By changing the source of bromide ion, we have recently demonstrated various valuable organic transformations.[17] In this letter, we report a very simple, efficient and environmentally benign synthesis of various 6,8-dibromoflavones and 8-bromoflavones starting from 2′-hydroxychalcones as shown in Scheme 1 as well as 5,7-dibromoaurones and 7-bromoaurone derivatives from 2′-acetoxychalcones as shown in Scheme 2.

For our investigation, various substituted chalcones were prepared by the literature procedures.[18] When 2′-hydroxychalcone (**1a**) was added to a solution of vanadium pentoxide, hydrogen peroxide and ammonium bromide, it gave 3,6,8-tribromo-4′,7-dimethoxyflavanone (**2a**) in 81% yield. Compound **2a** was then converted to the corresponding 6,8-dibromoflavone **3a** in 84% yield on treatment with ethanolic 0.2 M KOH solution. Similarly, the chalcone **1b** was transformed to the 6,8-dibromo-4′-benzyl-7-methoxyflavone (**3b**). Likewise, chalcones **1c**–**e** were converted to the corresponding 6,8-dibromoflavone derivatives **3c**–**e** in good yields (Table 1).

Interestingly, when 2′-hydroxychalcone **1f** was added to the above combination, it provided the 3,8-dibromo-5,7-dimethoxyflavanone (**2f**), which was readily converted to the 8-bromochrysin derivative **3f** in an 80% yield. From this observation, it is clear that bromination at position 6 is difficult due to the presence of two methoxy groups at the 4′- and 6′-positions on ring-A. Likewise, various 8-bromoflavones **3g**–**j** were synthesized from the corresponding 2′-hydroxychalcones (**1g**–**j**) in good yields as shown in Table 2.

Next, we were interested in the synthesis of bromoaurone derivatives and found that 2′-acetoxychalcones (**4a**–**c**) in the above reaction media gave **5a**–**c**, which were converted into the 5,7-dibromoaurones **6a**–**b** and 7-bromoaurone **6c** on treatment with 0.2 M KOH solution. The yields of the products are shown in Table 3. All the products were characterized by the usual spectroscopic techniques.[19]

In conclusion, we have accomplished the synthesis of various 6,8-dibromoflavones, 8-bromoflavones, 5,7-dibromoaurones and 7-bromoaurone from the



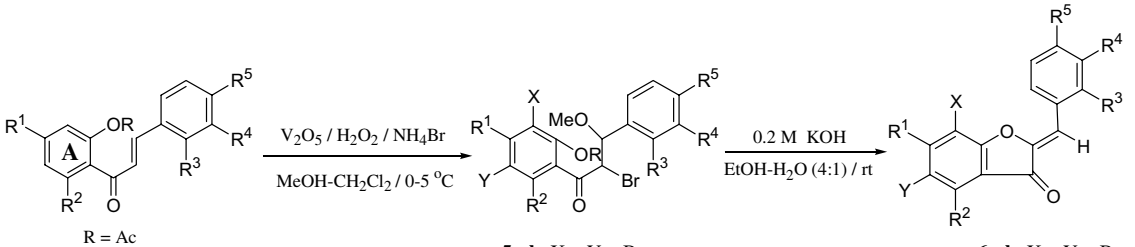
1a-j

2a-e: X = Y = Br
2f-j: X = Br, Y = H

3a-e: X = Y = Br
3f-j: X = Br, Y = H

1a: $R^1 = R^5 = OMe$, $R^2 = R^3 = R^4 = R^6 = H$
1b: $R^1 = OMe$, $R^5 = OBn$, $R^2 = R^3 = R^4 = R^6 = H$
1c: $R^1 = R^3 = R^5 = OMe$, $R^2 = R^4 = R^6 = H$
1d: $R^1 = R^4 = R^5 = OMe$, $R^2 = R^3 = R^6 = H$
1e: $R^1 = R^4 = R^5 = R^6 = OMe$, $R^2 = R^3 = H$
1f: $R^1 = R^2 = OMe$, $R^3 = R^4 = R^5 = R^6 = H$
1g: $R^1 = R^2 = R^5 = OMe$, $R^3 = R^4 = R^6 = H$
1h: $R^1 = R^2 = OMe$, $R^5 = OBn$, $R^3 = R^4 = R^6 = H$
1i: $R^1 = R^2 = R^3 = R^5 = OMe$, $R^4 = R^6 = H$
1j: $R^1 = R^2 = R^4 = R^5 = R^6 = OMe$, $R^3 = H$

Scheme 1.



R = Ac
4a-c

4a: $R^1 = R^3 = R^5 = OMe$, $R^2 = R^4 = H$
4b: $R^1 = R^4 = R^5 = OMe$, $R^2 = R^3 = H$
4c: $R^1 = R^2 = R^5 = OMe$, $R^3 = R^4 = H$

5a-b: X = Y = Br
5c: X = Br, Y = H

6a-b: X = Y = Br
6c: X = Br, Y = H

Scheme 2.

Table 1. Percentage yields of products

Entry	3,6,8-Tribromoflavanone **2**	% Yield	6,8-Dibromoflavone **3**	% Yield	Mp/°C
1a	**2a**	81	**3a**	84	220
1b	**2b**	65	**3b**	98	205
1c	**2c**	75	**3c**	88	209
1d	**2d**	79	**3d**	94	180
1e	**2e**	73	**3e**	92	188

Table 2. Percentage yields of products

Entry	3,8-Dibromoflavanone **2**	% Yield	Mp/°C	8-Bromoflavone **3**	% Yield	Mp/°C
1f	**2f**	77	230	**3f**	80	254 [lit. 253[11]]
1g	**2g**	85	210	**3g**	93	238 [lit. 236[11]]
1h	**2h**	69	165	**3h**	92	193
1i	**2i**	88	191	**3i**	94	217
1j	**2j**	74	180	**3e**	70	220

Table 3. Percentage yields of products **5** and **6**

Entry	Compound (**5**)	% Yield	Compound (**6**)	% Yield	Mp/°C
4a	**5a**	70	**6a**	85	206
4b	**5b**	75	**6b**	81	212
4c	**5c**	83	**6c**	83	253 [lit. 252[10]]

corresponding 2′-hydroxychalcones without involving molecular bromine. We have also demonstrated the synthesis of bromoaurones and bromoflavones exclusively, by tuning the bromination step.

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19. *General procedure*: A mixture of vanadium pentoxide (0.6 mmol, 110 mg) and aq 30% hydrogen peroxide (0.035 mmol, 4 mL) was stirred for 25–30 min at 0 °C until the colour changed from light orange to deep red. Then, ammonium bromide (2.24 mmol, 219 mg) was added and the reaction mixture was stirred for another 10 min. Subsequently, 2′-hydroxychalone (0.14 mmol) in dichloromethane (5 mL) was added. The reaction mixture was then stirred for a further 3.5 h at 0 °C. After completion of the reaction as monitored by TLC, it was extracted with dichloromethane (25 mL × 2) and the combined organic layer was washed with saturated sodium metabisulfite solution (2 mL). Finally, it was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent provided the crude residue, which was purified by column chromatography. The compound was eluted with a mixture of hexane–ethyl acetate (3:7) and the desired product was obtained either as a gummy liquid or solid.

Procedure for dehydrobromination: To a stirred solution of bromoflavanone **2** (0.10 mmol) in ethanol (5 mL) was added aqueous KOH (0.2 M, 0.5 mL) solution dropwise at room temperature. During addition of KOH solution, the reaction mixture turned yellow in colour. The reaction was complete within 25–30 min as monitored by TLC and was extracted with dichloromethane (25 mL × 2). The organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent and purification of the residue by silica gel column chromatography, [ethyl acetate–hexane (2:3)] gave the desired product, which was further recrystallized from methanol.

Spectroscopic data of 3,6,8-tribromo-4′,7-dimethoxyflavanone (**2a**): Gummy liquid, IR (neat): 1701 (C═O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.89 (d, 1H, J = 6.0 Hz, H-2), 5.73 (d, 1H, J = 6.0 Hz, H-3), 6.89 (d, 2H, J = 8.8 Hz, ArH), 7.27 (d, 2H, J = 9.2 Hz, ArH), 7.97 (s, 1H, ArH). Anal. Calcd for $C_{17}H_{13}Br_3O_4$: C, 39.19; H, 2.51. Found: C, 39.01; H, 2.56.

6,8-Dibromo-4′,7-dimethoxyflavone (**3a**): Mp: 220 °C, IR (KBr): 1650 (C═O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.70 (s, 1H, H-3), 7.04 (d, 2H, J = 8.8 Hz, ArH), 7.94 (d, 2H, J = 9.2 Hz, ArH), 8.08 (s, 1H, ArH). Anal. Calcd for $C_{17}H_{12}Br_2O_4$: C, 46.40; H, 2.75. Found: C, 46.21; H, 2.68.

3,8-Dibromo-4′,5,7-trimethoxyflavanone (**2g**): Mp: 211 °C; IR: 1685 (C═O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.84 (d, 1H, J = 4.8 Hz, H-3), 5.72 (d, 1H, J = 5.2 Hz, H-2), 6.16 (s, 1H, ArH), 6.85 (d, 2H, J = 8.4 Hz, ArH), 7.27 (d, 2H, J = 8.4 Hz, ArH). ^{13}C NMR (100 MHz, MeOH-d_4): δ 50.98, 55.63, 56.72, 57.07, 82.95, 90.44, 91.52, 104.69, 114.46 (2C), 127.70, 128.22 (2C), 157.83, 160.03, 162.35, 162.73, 181.70. Mass: m/z 472 (M^+). Anal. Calcd for $C_{18}H_{16}Br_2O_5$: C, 45.79; H, 3.42. Found: C, 45.54, H, 3.39.

8-Bromo-4′,5,7-trimethoxyflavone (**3g**): Mp: 238 °C [lit.[12] mp 236 °C], IR: 1634 (C═O) cm^{-1}. UV ($CHCl_3$): 325, 268 nm. ^1H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.04 (s, 3H, –OCH_3), 6.46 (s, 1H, ArH), 6.63 (s, 1H, H-3), 7.02 (d, 2H, J = 9.2 Hz, ArH), 7.96 (d, 2H, J = 9.2 Hz, ArH). Mass: m/z 392 (M^+). Anal. Calcd for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86. Found: C, 55.05; H, 3.80.

2-Bromo-1-(2-acetoxy-3-bromo-4,6-dimethoxyphenyl)-3-methoxy-3-(4-methoxyphenyl)-prop–1-one (**5c**): Mp: 216 °C; ^1H NMR (400 MHz, $CDCl_3$): 2.37 (s, 3H, $COCH_3$) 3.19 (s, 3H, $CHOCH_3$), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.60 (d, 1H, J = 10.0 Hz, H-2), 4.97 (d, 1H, J = 10.0 Hz, H-3), 6.52 (s, 1H, ArH), 6.90 (d, 2H, J = 8.8 Hz, ArH), 7.29 (d, 2H, J = 8.4 Hz, ArH). ^{13}C NMR (100 MHz, MeOH-d_4): δ 21.05, 54.48, 55.57, 56.93, 57.17, 57.66, 84.20, 94.59, 99.67, 113.86 (2C), 114.83, 129.43 (2C), 129.94, 148.48, 158.99, 159.68, 159.86, 167.65, 193.02 (C═O). Anal. Calcd for $C_{21}H_{22}Br_2O_7$: C, 46.18, H, 4.06. Found: C, 46.01; H, 4.00.

7-Bromo-4′,4,6-trimethoxyaurone (**6c**): Mp: 253 °C; UV ($CHCl_3$): 399, 329, 250 nm. ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.18 (s, 1H, ArH), 6.79 (s, 1H, H-3), 6.98 (d, 2H, J = 8.8 Hz, ArH), 7.89 (d, 2H, J = 8.9 Hz, ArH). ^{13}C NMR(100 MHz, $CDCl_3$): δ 55.44, 56.57, 56.96, 85.44, 90.69, 106.62, 112.22, 114.51 (2C), 125.01, 132.27 (2C), 146.41, 158.78, 160.90, 163.94, 164.35, 180.34 (C═O). Anal. Calcd for $C_{18}H_{15}BrO_5$: C, 55.26, H, 3.86. Found: C, 55.38; H, 3.92.