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An environmentally benign synthesis of aurones and flavones from 2′-acetoxychalcones using *n*-tetrabutylammonium tribromide†,‡

Gopal Bose,[a] Ejabul Mondal,[a] Abu T. Khan[a,*] and Manob J. Bordoloi[b]

[a]*Department of Chemistry, Indian Institute of Technology, Guwahati 781 039, India*
[b]*Natural Products Chemistry Division, Regional Research Laboratory, Jorhat 785 006, India*

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Abstract—A wide variety of aurones (**3a–f**) can be prepared exclusively from 2′-acetoxychalcones (**1a–f**) in high yields in two steps, by bromination using *n*-tetrabutylammonium tribromide (TBATB) in the presence of $CaCO_3$ in CH_2Cl_2–MeOH (5:2) at 0–5°C followed by cyclization of the brominated products **2a–f** on treating with 0.2 M ethanolic KOH solution at 0–5°C, respectively. In contrast various flavone derivatives **6a–f** can be obtained exclusively from compounds **1a–f** in fairly good yields, by brominating with the same reagent in CH_2Cl_2, followed by dehydrobromination and finally cyclization on treating with 0.1 M NaOMe solution.

Both aurones[1] [2-benzylidenebenzofuran-3(2*H*)-ones] and flavones,[2] which are structurally isomeric compounds, are widely distributed in nature. They play significant roles for the pigmentation of the flowers[3] in which they occur. On the other hand, flavones are well known in the literature due to their wide range of biological activities.[4] Among the various flavones, ring-A hydroxylated flavones in particular are of current interest due to their biological activities including inhibition of retroviral-reverse transcriptases,[5] protein–tyrosine kinases[6] and serine/threonine kinases.[7] They also possess anticancer[8] and chemo preventative activities.[9] Therefore, the synthesis of these compounds are still of interest largely on account of their biological activities.

The aurones are usually prepared from benzofuran-3(2*H*)-one, by acid- or base-catalyzed condensation with an appropriate aldehyde.[10] Similarly, there are a large number of methods available for the synthesis of flavones.[11] One of the methods which was originated by Kostanecki, based on cyclization of 2′-hydroxychalcone dibromides in aqueous alkali, is a useful route[12] for the synthesis of naturally occurring flavones. However, this procedure has certain disadvantages in that some of these dibromides give significant quantities of unwanted product aurones under certain conditions and sometimes fail to provide ring-A substituted flavones. Therefore, Donnelly and co-workers have investigated thoroughly the cyclization of 2′-acetoxychalcone dibromides[13] or α-bromo-2′-hydroxychalcones[14] to find out the probable reasons for failure. They have come to the conclusion that the formation of flavones is usually favored at low base concentrations as well as if there is no substituent at the position 3′ and 6′ or at any of the two positions of ring-A. Later on, Main et al. also studied[15] the cyclization of 2′-hydroxy-6′-methoxychalcone epoxide to find out whether the cyclization occurs preferentially either at the α or β position of the epoxide and came to similar conclusions that the cyclization takes place at the α-position preferably if there is a substituent on ring-A particularly at the 6′ position, which gives ultimately aurone hydrate. Unfortunately, it is not possible to access aurones exclusively by the above methods irrespective of the substitution pattern. The other problems which are associated with the preparation of 2′-hydroxychalcone dibromides include the use of molecular bromine which is hazardous, difficult to handle and which gives relatively low yields of the brominated products. It is also neces-

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* Corresponding author. Fax: +91-361-690 762; e-mail: atk@iitg.ernet.in

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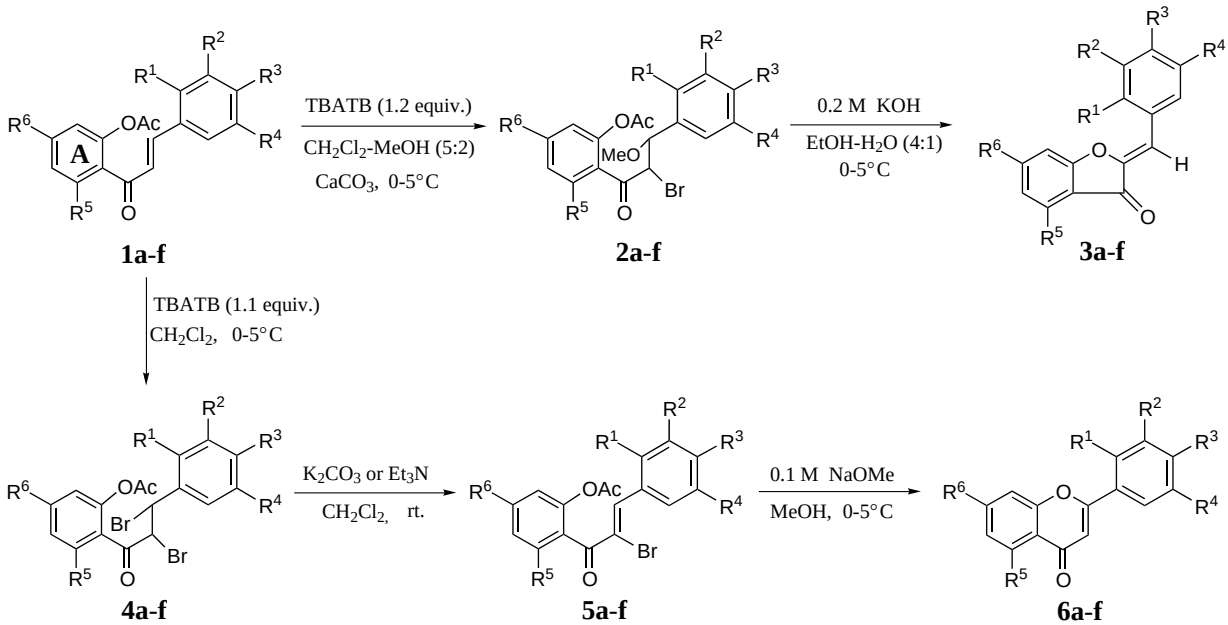
sary to maintain a stoichiometric ratio of reactants whilst carrying out the reaction. Therefore, what is needed is a methodology that is environmentally benign, clean, efficient and yet unambiguous.

Very recently, we disclosed that organic ammonium tribromides are useful reagents in organic synthesis.[16] From the unique behavior and properties of these reagents, we have conceived that they can be utilized for the selective synthesis of aurones and flavones depending upon the bromination steps. In this communication, we wish to report a very simple and practical synthesis of various aurones and flavones. Bromination of 2′-acetoxychalcone **1a** with *n*-tetrabutylammonium tribromide (TBATB, 1.2 equiv.) in the presence of $CaCO_3$ in a CH_2Cl_2–MeOH (5:2) mixture provided compound **2a** in 80 % yield (Scheme 1). Similarly, the compounds **1b–f** afforded **2b–f** in 75–85% yields, on bromination under identical conditions.

Aurones are obtained from compounds **2a–f** on treatment with 0.2 M KOH solution in EtOH (Table 1). All these compounds were fully characterized by ^{1}H NMR, ^{13}C NMR and elemental analyses.[17] The compounds **1a–f** on bromination with the same reagent in CH_2Cl_2 gave the brominated products **4a–f** in good yields. Various flavones (**6a–f**) were obtained in good yields from the brominated products **4a–f** by dehydrobromination followed by cyclization on treatment with 0.1 M sodium methoxide solution (Table 1). All the products were characterized by usual spectroscopic techniques.[18]

The formation of the cyclized product aurones **3a–f** or flavones **6a–f** can be explained as follows. The forma-



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

Scheme 1.

Table 1. Percentage yields of products

Entry	Product **2**	% Yield	Aurone **3**	% Yield	Dibromo product (**4**)	% Yield	α-Bromo chalcone (**5**)	% Yield	Flavone (**6**)	% Yield
1a	**2a**	80	**3a**	85	**4a**	70	**5a**	80	**6a**	78
1b	**2b**	75	**3b**	91	**4b**	78	**5b**	90	**6b**	70
1c	**2c**	85	**3c**	87	**4c**	75	**5c**	83	**6c**	88
1d	**2d**	84	**3d**	95	**4d**	80	**5d**	85	**6d**	74
1e	**2e**	76	**3e**	86	**4e**	80	**5e**	88	**6e**	65
1f	**2f**	80	**3f**	87	**4f**	75	**5f**	80	**6f**	60

tion of aurone is favored because Br is a better leaving group in comparison to OMe, so the cyclization takes place exclusively at the α-position. In contrast the formation of the flavones from compounds **5a–f** takes place via Michael type reactions.

In conclusion, we have accomplished the synthesis of ring-A hydroxylated naturally occurring flavone derivatives such as the methyl ether of apigenin (**6a**), norartocarpetin (**6c**), tricetin (**6d**), luteolin (**6e**) and the naturally occurring aurone derivative aureusidin (**3e**). We have also demonstrated the synthesis of aurones and flavones exclusively by tuning the bromination step. Other organic ammonium tribromides can also be used for the bromination reactions, which are under investigation.

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17. **Spectroscopic data of 2a**: crystalline solid, mp: 122–123°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, $COCH_3$), 3.17 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3), 4.65 (d, 1H $J=9.6$ Hz, C*H*OMe), 5.01 (d, 1H, $J=9.6$ Hz, COC*H*Br), 6.29 (s, 1H, ArH), 6.38 (s, 1H, ArH), 6.90 (d, 2H, $J=8.2$ Hz, ArH), 7.31 (d, 2H, $J=8.2$ Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.02, 169.21, 163.14, 159.96, 159.78, 151.24, 130.22, 129.35 (2C), 114.83, 113.60 (2C), 101.37, 96.77, 84.16, 57.42, 56.16, 55.69, 55.24, 54.33, 20.91. Anal. calcd for $C_{21}H_{23}BrO_7$: C, 53.97; H, 4.96. Found C, 53.43, H, 4.92.
Spectroscopic data of 3a: Yellow crystalline solid, mp: 167–168°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.94 (s, 3H, -OCH_3), 6.15 (d, 1H, $J=1.6$ Hz, ArH), 6.36 (d, 1H, $J=1.6$ Hz, ArH), 6.73 (s, 1H, =C*H*Ph), 6.94 (d, 2H, $J=8.7$ Hz, ArH), 7.80 (d, 2H, $J=8.7$ Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.53, 168.84, 168.71, 160.62, 159.41, 146.84, 132.84 (2C), 125.90, 125.39, 114.37 (2C), 110.90, 93.97, 89.24, 56.18, 56.02, 55.32. Anal. calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found C, 68.99; H, 4.98.
18. **Spectroscopic data of 5a**: gummy liquid, ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.10 (s, 3H, $COCH_3$), 3.74 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, -OCH_3), 6.31 (d, 1H, $J=2.1$ Hz, ArH), 6.38 (d, 1H, $J=2.1$ Hz, ArH), 6.92 (d, 2H, $J=9.0$ Hz, ArH), 7.72 (s, 1H, =C*H*Ph), 7.89 (d, 2H, $J=9.0$ Hz, ArH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 187.67, 168.74, 162.07, 161.57, 158.64, 149.47, 143.66, 132.91 (2C), 126.17, 122.38, 114.12, 113.87 (2C), 100.26, 96.69, 56.05, 55.62, 55.34, 20.68. Anal. calcd for $C_{20}H_{19}BrO_6$: C, 55.18; H, 4.40. Found C, 55.03; H, 4.32.
Spectroscopic data of 6a: crystalline solid, mp: 155–156°C (lit. 156–157°C), ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, -OCH_3), 6.30 (d, 1H, $J=2.3$ Hz), 6.50 (d, 1H, $J=2.3$ Hz, ArH), 6.57 (s, 1H, =CH-), 6.93 (d, 1H, $J=9.0$ Hz, ArH) 7.75 (d, 2H, $J=9.0$ Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.46, 163.95, 162.06, 160.79, 159.74, 130.00, 127.54 (2C), 123.63, 114.27 (2C), 108.94, 107.29, 96.06, 92.78, 56.29, 55.66, 55.36. Anal. calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found C, 68.99; H, 4.98.