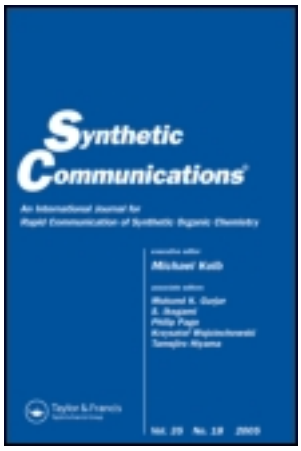

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A CONVENIENT SYNTHESIS OF 3-BROMOFLAVONES

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A CONVENIENT SYNTHESIS OF 3-BROMOFLAVONES

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ABSTRACT

The reaction of flavones with 2,4,4,6-tetrabromo-2,5-cyclohexadienone(**1**) gave the corresponding 3-bromoflavones under the mild reaction condition. Flavones containing easily oxidizable functional groups were also brominated without deleterious oxidation products.

The standard method of α-bromination of enone system is the reaction of enones with various bromine atom sources, such as molecular bromine, *N*-bromosuccinimide, pyridinium tribromide and copper(II) bromide in the absence or presence of catalysts, respectively.[1–5] Using these reagents, α,β-unsaturated carbonyl compounds are selectively transformed into the corresponding α- or α'-bromo derivatives. Although these reagents are commonly used in organic synthesis, a powerful Br source, such as Br_2 in AcOH or in base, was not able to be used for the bromination of a deactivated system containing easily oxidizable substituent because of its powerful oxidation potential; an undesired oxidation by-product also was formed.

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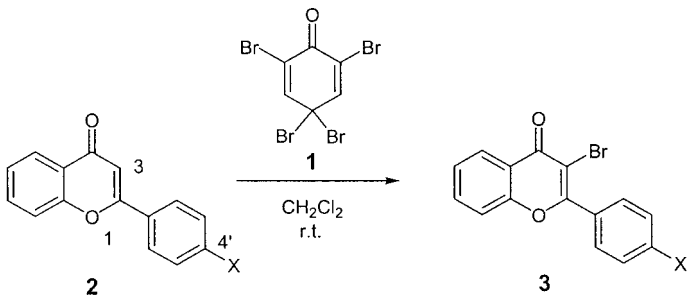
In order to minimize the side reaction, it was necessary to find a new reagent with fine-tuned brominating power.

In our ongoing program for a search of biologically active compounds, 3-bromoflavones were necessary as intermediates and could be obtained using the pyridinium bromide perbromide/pyridine as a mild brominating reagent. However, in the reaction of flavones containing sulfide side chains with this reagent, undesired sulfoxide derivatives were obtained as a major product.[6] In order to minimize an undesired product and find a more efficient brominating reagent, we have investigated the brominating power of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**1**), which has been used for the aromatic bromination,[7] brominative cyclization of polyene,[8] selective α'-bromination of α,β-unsaturated ketones,[9] and oxidation of thiols to disulfides.[10] In this communication, we report an efficient, simple, and practical method for the conversion of flavones to α-bromoflavone derivatives using reagent **1** under the mild reaction conditions.

First, when the simple flavones were treated with compound **1** in CH_2Cl_2 at room temperature, 3-bromoflavones were obtained. As shown in Table 1, flavone (**2a)** was transformed into 3-bromoflavone **(3a**) in 63% yield at room temperature. Bromination of electron donating 4′-methoxy substituted flavone **2b** proceeded fast and gave 3-bromo derivative **3b** in good yield. In the case of an electron withdrawing group such as 4′-fluoro, 4′-methylsulfonyl substituted flavones **2c**, **2d**, and 3-bromo derivatives were obtained in low yield and needed a prolonged reaction time. And the reaction of highly electron withdrawing nitro substituted flavone **2e** with compound **1** was not proceeded at all in boiling chloroform. In addition, 1-thioflavone afforded 3-bromo-1-thioflavone in high yield under the standard reaction condition. The above results apparently indicate that C-4′ substituent of a flavone B ring plays an important role in electrophilic attack of Br at C-3.



Chem 1.

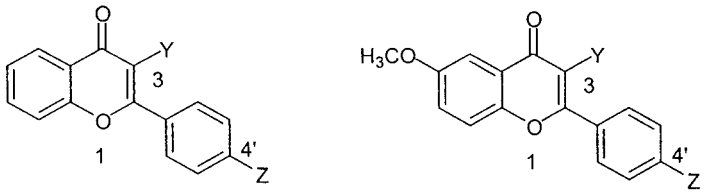
Table 1. Bromination of Flavones with 2,4,4,6-Tetrabromo-2,5-cyclohexadienone (**1**) in CH_2Cl_2 at Room Temperature

Substrates	X	Products	Time (h)	Yields[a] (%)
2a	H	**3a**	78	63
2b	OCH_3	**3b**	2	87
2c	F	**3c**	72	50
2d	SO_2CH_3	**3d**	120	26
2e	NO_2	**3e**	12	NR[b]
1-Thioflavone		3-Bromo-1-thioflavone	24	89

[a]Isolated yields.
[b]In boiling $CHCl_3$.

By substitution of an electron donating group at C-4′ or sulfur in place of oxygen at C-1, the reaction rate and product yield were improved. This fact is closely related to the increased electron density at the C-3 position by the C-4′ or C-1 substitutent. In case of flavone **2f** containing a sulfide side chain, bromination using compound **1** under the standard reaction condition afforded 3-bromoflavone **3f** without side products such as sulfoxide and an A ring bromination product (Table 2, Entry 1). On the contrary, when the bromination was performed in the presence of *N*-bromosuccinimide (NBS) or molecular bromine, 3-bromo derivatives were obtained in low yield (Entry 2) or oxidation products (Entry 3) were obtained major component.[6] Also, in the presence of water, sulfoxide was obtained as the sole product[11] but not detected the 3-bromo derivative (Entry 4).

Although compound **1** has been used for aromatic ring bromination, the reaction of flavone **2g**, having an electron donating methoxy group at



2f Y = H , Z = SCH_3
3f Y = Br , Z = SCH_3
4 Y = H , Z = $SOCH_3$
5 Y = Br , Z = $SOCH_3$

2g Y = H , Z = SCH_3
3g Y = Br , Z = SCH_3

Chem 2.

Table 2. Reaction of 4′-(Methylthio)flavones with Various Br Sources

Entry	Substrates	Br Source	Products	Time (h)	Yields[a] (%)
1	**2f**	**1**	**3f**	2	80
2	**2f**	**NBS**	**3f**	7	42[b]
3	**2f**	**Br_2**	**4 + 5**	4	37 + 33
4	**2f**	**1**	**4**	17	80[c]
5	**2g**	**1**	**3g**	2	70

[a]Isolated yields.
[b]In boiling $CHCl_3$.
[c]In 80% aqueous THF.

C-6 of A ring with **1** afforded 3-bromoflavone **3g** in 70% yield and no A ring bromination took place (Entry 5).

In conclusion, we developed a mild and convenient method for the bromination of flavones having various substituents using 2,4,4,6-tetrabromo-2,5-cyclohexadienone without an undesired side reaction product.

Typical experimental procedure: To a solution of the flavone (**2a**) (0.2 g, 0.9 mmol) in dry CH_2Cl_2(10 ml) under nitrogen was added 2,4,4,6-tetrabromo-2,5-cyclohexadienone(**1**) (0.53 g, 1.3 mmol) at room temperature. After stirring at room temperature for 78 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed with saturated aqueous $NaHCO_3$ solution (20 ml) and brine (20 ml). The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the organic layer, the residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to give 3-bromoflavone (**3a**) (0.17 g, 63%). Their spectroscopic data are as follows.

3a: M.p. 123–124°C (lit.[5] m.p. 126°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.60 (m, 5H), 7.70–7.76 (m, 1H), 7.84–7.88 (m, 2H), 8.31 (dd, 1H, $J = 7.8$, 1.5 Hz).

3b: M.p. 139–141°C (lit.[6] m.p. 140–141°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.02–7.07 (m, 2H), 7.43–7.53 (m, 2H), 7.68–7.75 (m, 1H), 7.86–7.92 (m, 2H), 8.30 (dd, 1H, $J = 7.8$, 1.5 Hz).

3c: M.p. 167–169°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.30 (m, 2H), 7.44–7.53 (m, 2H), 7.70–7.78 (m, 1H), 7.85–7.92 (m, 2H), 8.30 (dd, 1H, $J = 7.8$, 1.5 Hz); MS (70 eV) m/z (rel. intensity) 120 (78), 183 (40), 239 (62), 290 (41), 292 (40), 318 (M^+, 100), 320 ($M^+ + 2$, 99); Anal. calcd for $C_{15}H_8BrFO_2$: C, 56.45; H, 2.53. Found: C, 56.10; H, 2.47.

3d: M.p. 205–208°C (lit.[6] m.p. 207–209°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 7.48–7.54 (m, 2H), 7.73–7.80 (m, 1H), 8.05–8.16 (m, 4H), 8.32 (dd, 1H, $J = 8.7$, 1.8 Hz).

3-Bromo-1-thioflavone: M.p. 130–132°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.70 (m, 8H), 8.60–8.64 (m, 1H); MS(70 eV) m/z (rel. intensity) 136 (32), 165 (51), 208 (46), 237 (58), 288 (35), 290 (36), 316 (M^+, 99), 318 ($M^+ + 2$, 100); Anal. calcd for $C_{15}H_9BrOS$: C, 56.80; H, 2.86. Found: C, 56.70; H, 2.83.

3f: M.p. 159–160°C (lit.[6] m.p. 160–161°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 7.34–7.40 (m, 2H), 7.44–7.52 (m, 2H), 7.68–7.75 (m, 1H), 7.80–7.85(m, 2H), 8.29 (dd, 1H, $J = 8.1$, 1.5 Hz).

3g: M.p. 152–154°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.93 (s, 3H), 7.27–7.46 (m, 4H), 7.62–7.64 (m, 1H), 7.78–7.83 (m, 2H); MS (70 eV) m/z (rel. intensity) 150 (44), 226 (23), 228 (19), 346 (5), 348 (9), 376 (M^+, 98), 378 ($M^+ + 2$, 100); Anal. calcd for $C_{17}H_{13}BrO_3S$: C, 54.12; H, 3.47. Found: C, 54.40; H, 3.68.

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