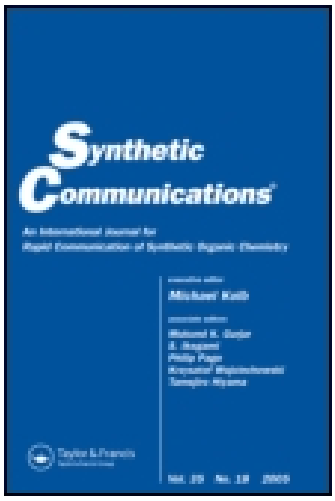

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SYNTHESIS OF 3-BROMO DERIVATIVES OF FLAVONES

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SYNTHESIS OF 3-BROMO DERIVATIVES OF FLAVONES

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ABSTRACT

Various 3-halo flavones were prepared by reaction of the corresponding flavone derivatives with $R_4NBr/PhI(OAc)_2$ system under mild reaction conditions.

Halogenated compounds are important intermediates for converting efficiently into other functionality by simple chemical transformations.[1–3] They are usually prepared by using molecular halogens.[4,5] But molecular halogens can be difficult to manipulate and they have environmental drawbacks. To overcome these difficulties, alternative methods have been developed such as HX/H_2O_2,[6,7] NBS/PhI(OH)(OTs),[8,9] $TiCl_4$/*tert*-BuOOH,[10]

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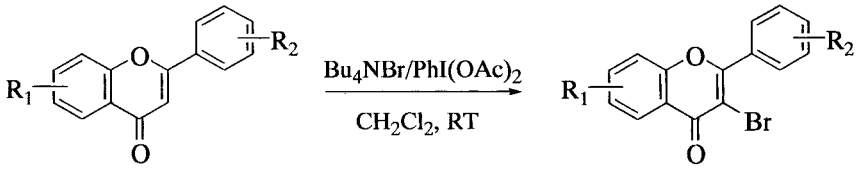
NaX/Oxone,[11] TMSX/PhI(OAc)$_2$[12–14] and KBr/NaBO$_3$.[15] The halogen or positive halogen species are generated in situ and they are used for halogenation of organic substrate. Recently, Kirschning[16,17] reported that a combination of Et$_4$NBr and PhI(OAc)$_2$ was used in a bromoacetoxylation of olefin. But it has not been used for a bromination of α,β-unsaturated carbonyl compounds. As a flavone has a α,β-unsaturated ketone moiety, it was interested to make its 3-bromo derivatives. 3-Bromo flavones are important intermediates for the C-3 modification. However, there are few reports on methods to prepare these compounds. In previous reports, molecular bromine is generally used in various reaction conditions.[18–24] As an alternative of molecular bromine, R$_4$NBr/PhI(OAc)$_2$ system is a good bromination source for flavone. In this communication, we wish to report a selective C-3 bromination of flavones by R$_4$NBr/PhI(OAc)$_2$ system under mild conditions (Scheme 1).

To determine optimal reaction conditions, a series of experiments were performed on the substrate **1a** with several alkyl ammonium salts. The results are summarized in Table 1. Treatment of flavone **1a** with 3 equivalent of PhI(OAc)$_2$ and 3 equivalent of Me$_4$NBr in CH_2Cl_2 at room temperature afforded the corresponding 3-bromo flavone **2a** in 75% yield (Entry 1 in



1 **2**

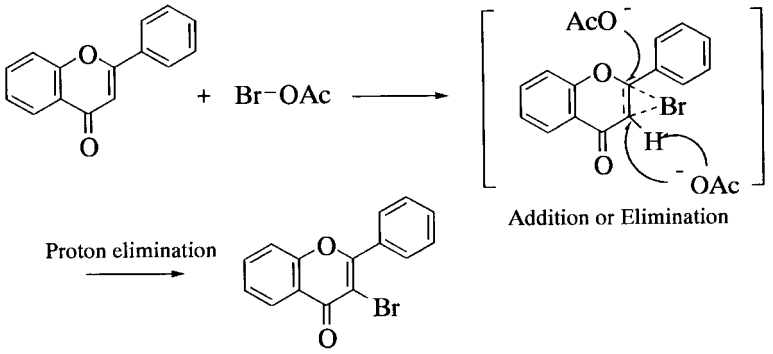
Scheme 1.

Table 1. Reaction Conditions for Bromination of Flavone **1a**

Entry	Ammonium Salt[a]	Base	Time (h)	Yield (%)[b]
1	Me$_4$NBr(3)	None	10	75
2	Et$_4$NBr(3)	None	10	76
3	Bu$_4$NBr(3)	None	8	84
4	Bu$_4$NBr(3)	Pyridine	8	80

[a]With PhI(OAc)$_2$ (3 equiv.), CH_2Cl_2, RT. The molar equivalents are given in parentheses. [b]Isolated yields.

Table 1). None of the aromatic bromination or bromoacetoxylation compounds were detected in crude product. Of the alkyl ammonium salt tested, the best choice was Bu_4NBr. In the presence of base, there was no noticeable difference in both reaction time and yield (Entry 4 in Table 1). The initial step in this reaction is the formation of bromonium intermediate by addition of Br-OAc to double bond. There are two reaction pathways such as proton elimination and addition of acetate anion. The pathway of elimination must be faster than that of addition (Scheme 2).

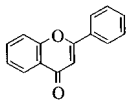
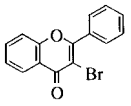
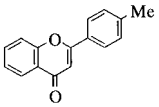
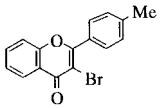
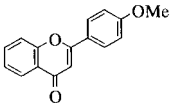
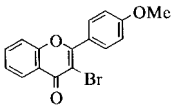
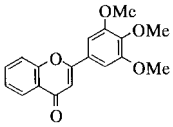
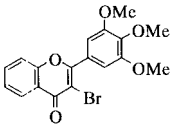
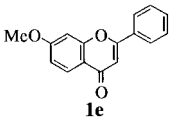
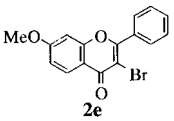
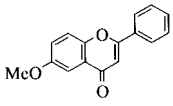
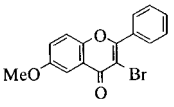
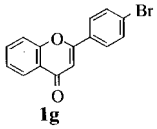
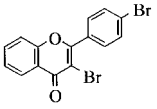
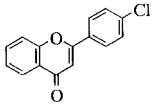
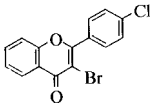


Scheme 2.

Alternatively, treatment of **1a** under the same condition using MeOH as solvent, bromomethoxylation product was obtained as the sole product.[25] In case of Br-OMe, addition pathway was preferred. We extended this optimized reaction condition to other flavones. The results are summarized in Table 2. The flavones **1b–e** and **1f** which have methyl or methoxy substituent in the A or B ring gave the 3-bromo flavones in the moderate to high yield. In the case of **1b**, **1c** and **1d** which have electron-donating groups at *para* position in B ring, give the 3-bromo derivatives in high yields. The stabilizing effect to the cationic intermediate increased the yields. However, the flavone **1g** bearing a bromo substituent converted into corresponding 3-bromo flavone in low yield (Entry 7 in Table 2). In contrast to above cases, the destabilizing effect of bromo substituent decreased the rate of the addition of Br-OAc and the elimination process. Finally, for 4-chloro flavone **1h** in the same condition, bromo flavone **2h** was obtained in 52% yield (Entry 8).

In summary, we have developed a mild and convenient procedure for the preparation of 3-bromo derivatives of flavones.

Table 2. Synthesis of 3-Bromo Derivatives of Flavones[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1a**	8	 **2a**	84
2	 **1b**	7	 **2b**	89
3	 **1c**	7	 **2c**	92
4	 **1d**	8.5	 **2d**	89
5	 **1e**	9	 **2e**	78
6	 **1f**	8	 **2f**	80
7	 **1g**	10	 **2g**	50
8	 **1h**	10	 **2h**	52

[a]All the reactions were run with Bu_4NBr (3 equiv.) and $PhI(OAc)_2$ (3 equiv.) in CH_2Cl_2. [b]The yields are for isolated compounds.

EXPERIMENTAL

Materials

$PhI(OAc)_2$ (98%) and Bu_4NBr (98%) were purchased from Aldrich Chemical Co.

Typical Procedure

3-Bromo-2-phenyl-4H-chromen-4-one (2a):[20,24] $PhI(OAc)_2$ (434 mg, 1.35 mmol) was suspended in anhydrous CH_2Cl_2 (5 ml) under atmosphere of nitrogen at room temperature. Bu_4NBr (435 mg, 1.35 mmol) was added and the mixture was stirred at room temperature for 30 min. The flavone **1a** (100 mg, 0.45 mmol) in anhydrous in CH_2Cl_2 (2 ml) was added and the mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and aqueous portion was separated and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by SiO_2 column chromatography (EtOAc/hexanes 1 : 2, $R_f = 0.64$) to give **2a** (113 mg, 84%). M.p. 124–125°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (dd, 1H, $J = 7.8$, 1.5 Hz), 7.84–7.90 (m, 2H), 7.70–7.75 (m, 1H), 7.44–7.57 (m, 5H). MS (*m*/*e*) 302 ($M^+ + 2$), 300 (M^+), 272, 221, 165, 120 (base peak), 92.

3-Bromo-2-(4-methylphenyl)-4H-chromen-4-one (2b):[24] TLC, SiO_2, EtOAc/hexanes 1 : 2, $R_f = 0.82$. M.p. 165–166°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (dd, 1H, $J = 8.1$, 1.5 Hz), 7.79 (d, 2H, $J = 8.4$ Hz), 7.71 (m, 1H), 7.48 (m, 2H), 7.33 (d, 2H, $J = 8.4$ Hz), 2.46 (s, 3H). MS (*m*/*e*) 316 ($M^+ + 2$), 314 (M^+), 286, 235 (base peak), 120, 89.

3-Bromo-2-(4-methoxyphenyl)-4H-chromen-4-one (2c):[24] TLC, SiO_2, EtOAc/hexanes 1 : 2, $R_f = 0.43$. M.p. 140–142°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (dd, 1H, $J = 7.8$, 1.5 Hz), 7.86 (d, 2H, $J = 8.7$ Hz), 7.68–7.74 (m, 1H), 7.42–7.50 (m, 2H), 7.05 (d, 2H, $J = 8.7$ Hz), 3.90 (s, 3H). MS (*m*/*e*) 332 ($M^+ + 2$), 330 (M^+), 302, 251 (base peak), 210, 195, 152.

3-Bromo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-4-one (2d): TLC, SiO_2, EtOAc/hexanes 1 : 2, $R_f = 0.36$. M.p. 155–156°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (dd, 1H, $J = 7.8$, 1.5 Hz), 7.76 (m, 1H), 7.54 (m, 2H), 7.10 (s, 2H), 3.95 (s, 3H), 3.94 (s, 6H). MS (*m*/*e*) 392 ($M^+ + 2$), 390 (M^+, base peak), 375, 347, 253, 121. Anal. calcd for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86. Found: C, 55.20; H, 3.78.

3-Bromo-7-methoxy-2-phenyl-4H-chromen-4-one (2e): TLC, SiO_2, EtOAc/hexanes 1 : 2, $R_f = 0.52$. M.p. 151–152°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, 2H, $J = 8.7$ Hz), 7.86 (m, 2H), 7.56 (m, 3H),

7.04 (d, 1H, $J = 8.7$ Hz), 6.89 (s, 1H), 3.92 (s, 3H). MS (*m*/*e*) 332 ($M^+ + 2$), 330 (M^+), 302, 287, 251 (base peak), 195, 152, 122. Anal. calcd for $C_{16}H_{11}BrO_3$: C, 58.03; H, 3.35. Found: C, 57.97; H, 3.27.

3-Bromo-6-methoxy-2-phenyl-4H-chromen-4-one (2f):[24] TLC, SiO_2, EtOAc/hexanes 1 : 2, $R_f = 0.50$. M.p. 123–125°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83–7.86 (m, 2H), 7.43–7.62 (m, 5H), 7.27–7.33 (m, 1H), 3.93 (s, 3H). MS (*m*/*e*) 332 ($M^+ + 2$) 330 (M^+), 252, 150 (base peak), 79.

3-Bromo-2-(4-bromophenyl)-4H-chromen-4-one (2g): TLC, SiO_2, EtOAc/Hexanes 1 : 2, $R_f = 0.77$. M.p. 188–189°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (dd, 1H, $J = 7.8$, 1.5 Hz), 7.67–7.77 (m, 5H), 7.26–7.51 (m, 2H). MS (*m*/*e*) 382 ($M^+ + 4$) 380 ($M^+ + 2$), 378 (M^+), 352, 220, 120 (base peak). Anal. calcd for $C_{15}H_8Br_2O_2$: C, 47.41; H, 2.12. Found: C, 47.35; H, 2.08.

3-Bromo-2-(4-chlorophenyl)-4H-chromen-4-one (2h): TLC, SiO_2, EtOAc/hexanes 1 : 2, $R_f = 0.55$. M.p. 179–180°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (dd, 1H, $J = 7.8$, 1.5 Hz), 7.64–7.73 (m, 5H), 7.24–7.52 (m, 2H). MS (*m*/*e*) 338 ($M^+ + 4$), 336 ($M^+ + 2$) 334 (M^+), 306, 255, 281, 207, 120 (base peak). Anal. calcd for $C_{15}H_8BrClO_2$: C, 53.69; H, 2.40. Found: C, 53.58; H, 2.32.

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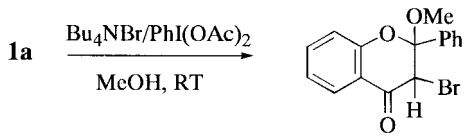

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