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A Selective Transformation of Flavanones to 3-Bromoflavones and Flavones Under Microwave Irradiation

Zhongzhen Zhou, Peiliang Zhao, Wei Huang, Guangfu Yang*

Key Laboratory of Pesticide & Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, People's Republic of China
Fax: (+86)-27-6786-7141, e-mail: gfyang@mail.ccnu.edu.cn

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Abstract: This paper presents the first report of a highly selective transformation of flavanones to 3-bromoflavones or flavones by microwave irradiation of the corresponding flavanone reactants and *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of 2,2′-azobis(isobutyronitrile) (AIBN). The combination of good to excellent yields, shorter reaction time (10 min), and high levels of functional group compatibility make this an attractive synthetic approach to 3-bromoflavones and flavones.

Keywords: 3-bromoflavones; *N*-bromosuccinimide; flavanones; flavones; microwave irradiation

3-Substituted flavones are of considerable interest because of their widespread occurrence in nature as well as their biological activities.[1] Many methods have been developed for the synthesis of 3-substituted flavones,[2] most of which involve C-3 modification of flavones by simple chemical transformations *via* 3-haloflavones, especially 3-bromoflavones.[2c–e] Among various methods reported to date,[3] 3-bromoflavones have been prepared by brominating flavones using Br_2/AcOH,[3b] $Bu_4NBr/PhI(OAc)_2$,[3c] 2,4,4,6-tetrabromo-2,5-cyclohexadienone[3d] or pyridinium bromide perbromide/pyridine system.[3e] However, most of these methods are of limited use because they have low yields and give mixtures of products containing different A-ring bromination patterns. Furthermore, these procedures require prolonged reaction times, toxic metal ions, or reagents that are not commercially available. We noticed that flavones have been prepared by the dehydrogenation of flavanones for many years,[4] but could find no report of the synthesis of 3-bromoflavones directly using flavanones as starting materials. As one of the most useful and convenient brominating reagents, *N*-bromosuccinimide (NBS) has been commonly used to transform α,β-unsaturated carbonyl compounds into the corresponding α- or α′-bromo derivatives.[5] Although the dehydrogenation of flavanones to form the corresponding flavones using NBS as a brominating reagent has been reported,[4j, k] we could find no report of the direct transformation of flavanones into 3-bromoflavone by NBS-bromination.

Microwave irradiation has emerged as a powerful technique for promoting a variety of chemical reactions.[6] The main benefits of performing reactions under microwave irradiation conditions are significant rate-enhancements and higher product yields. As part of an ongoing program in our laboratory to synthesize a variety of 3-substituted flavones under mild conditions, we herein report the first example of a highly selective method for synthesizing 3-bromoflavones and flavones *via* microwave-assisted bromination of the corresponding flavanones using NBS.

As a starting point for the development of our methodology, we first examined the dehydrogenation of flavanones to form the corresponding flavones using NBS as a brominating reagent under microwave irradiation. The reaction of 4′-chloroflavanone with an equimolar NBS in CCl_4 was chosen as a model to optimize the reaction condition. Microwave reactions were performed in sealed heavy-walled Pyrex tubes under controlled conditions in a safe and reproducible manner. Single mode microwave irradiation was used at a fixed temperature, pressure, and irradiation power during the reaction time by automatic power control. The results of optimization experiments are summarized in Table 1.

As shown in Table 1, raising the reaction temperature from 80 to 100 °C for the same irradiation time of 10 min improved the yield of 4′-chloroflavone remarkably from 4% to 96%. On further increases of the temperature above 100 °C, the high yield was maintained even when the reaction temperature was raised to 130 °C. Moreover, for the reaction at 100 °C, prolonging the reaction time from 10 min to 20 min did not affect the yield

Table 1. Optimization of the bromination of 4′-chloroflavanone.

No	Temp. [°C]	Time [min]	Yield [%][a]
1	80	10	4
2	90	10	34
3	100	10	96
4	110	10	95
5	120	10	95
6	130	10	95
7	100	5	70
8	100	15	95
9	100	20	96

[a] The yield was measured by HPLC.

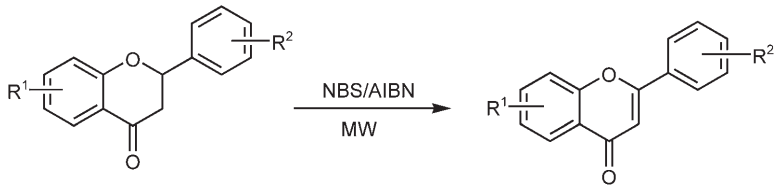
whereas reducing the reaction time to 5 min caused the yield to decrease considerably. The increasing demand for clean and efficient "eco-friendly" chemical syntheses has increased our interest in solvent-free reactions which, when combined with microwave irradiation, have advantages from both economic and environmental standpoints.[7] Hence we attempted the solvent-free synthesis of flavones by NBS bromination of flavanones under microwave irradiation. Unfortunately, the mixture of NBS and flavanones in a molar ratio of 1:1 did not react at 100 °C under microwave irradiation and, when the temperature was increased to 140 °C, the products were so complex that it is very difficult to obtain the desired flavones. Further optimization of the solvent (e.g., CH_2Cl_2, $CHCl_3$ and CCl_4) indicated that CCl_4 gave the best results. Thus, the optimal conditions for the synthesis of flavones are 100 °C for 10 min using CCl_4 as solvent. These conditions were used for the transformation of other flavanones bearing various substituents. The results obtained are shown in Table 2, which also shows the results of control experiments in which the reactions were carried out under conventional heating.

The results in Table 2 indicate that the proposed methodology gives good to excellent yields for a range of substrates. The exceptions to this are 4′-methylflavone and 6-methylflavone (Table 2, entries 4 and 8), which were obtained in moderate yield and showed a tendency to undergo bromination of the methyl group on the phenyl-ring. This latter tendency has been observed previously using other methods for brominating flavanones.[3] Furthermore, the reaction under microwave irradiation required only 10 min, compared to 12 h for the conventional heating technique.

We were keen to see if it was possible to further brominate flavones to 3-bromoflavones. In the presence of catalytic amounts of 2,2′-azo-bis(isobutyronitrile) (AIBN), refluxing of a mixture of flavone and NBS in a 1:2 molar ratio in CCl_4 for 24 hours gave 3-bromoflavone in 50% yield. This finding prompted us to develop a strategy for directly synthesizing 3-bromoflavones from flavanones under microwave irradiation.

Initial optimization studies were carried out using a variety of brominating agents (e.g., $CuBr_2$, Br_2/pyridine,

Table 2. Microwave-assisted dehydrogenation of flavanones with NBS.

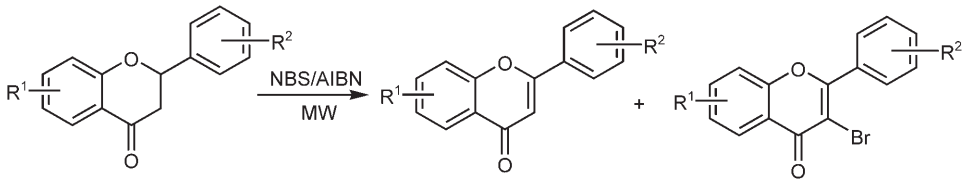


1 2

No	R^1	R^2	Microwave irradiation		Traditional heating	
			Time [min]	Yield [%][a]	Time [h]	Yield [%][a]
1	H	H	10	90 (88)	16	65 (61)
2	H	3′-Cl	10	98 (95)	12	74 (70)
3	H	4′-Cl	10	96 (92)	12	79 (74)
4	H	4′-Me	10	73 (69)	12	60 (55)
5	H	3′-Br	10	97 (94)	12	75 (70)
6	H	4′-MeO	10	89 (85)	12	62 (58)
7	7-MeO	H	10	89 (87)	12	65 (62)
8	6-Me	H	10	73 (69)	12	62 (59)
9	6-Cl	H	10	97 (95)	12	64 (60)
10	7-MeO	4′-Cl	10	97 (94)	12	66 (63)

[a] The yield was measured by HPLC; the value in parentheses is the isolated yield.

Table 3. Microwave-assisted preparation of 3-bromoflavones **3**.



1 **2** **3**

No.	R^1	R^2	Solvent-free Microwave[a]				Conventional Refluxing		
			Temp. [°C]	Time [min]	Yield [%][b]		Time [h]	Yield [%][b]	
					2	**3**		**2**	**3**
1a	H	H	140	10	0	100 (98)	24	10	70 (65)
1b	H	3′-Cl	140	10	7	93 (90)	24	28	54 (51)
1c	H	4′-Cl	140	10	6	94 (91)	24	8	80 (77)
1d	H	3′-Br	140	10	2	98 (95)	24	30	52 (50)
1e	H	4′-MeO	140	10	6	94 (93)	24	26	55 (51)
1f	7-MeO	H	140	10	9	91 (87)	24	15	61 (58)
1 g	6-Cl	H	140	10	5	95 (94)	24	18	66 (64)
1 h	7-MeO	4′-Cl	140	10	9	91 (89)	24	16	65 (63)

[a] The irradiation power is 150–300 W.
[b] The yield was measured by HPLC; the value in parentheses is the isolated yield.

2,4,4,6-tetroabromo-2,5-cyclohexadienone, pyridinium bromide perbromide, NBS/AIBN), the 1:3 (molar ratio) flavanones/NBS system was found to be most effective for the transformation of flavanones to 3-bromoflavones. Further optimizations were carried out by varying the reaction temperature from 100 °C to 160 °C, the irradiation time from 10 min to 25 min, and by using various solvents (e.g., CH_2Cl_2, $CHCl_3$, CCl_4, and solvent-free). These experiments indicated that the optimized reaction conditions for the clean, rapid and efficient transformation of flavanones were the solvent-free reaction of flavanones **1** (1 equiv.) with NBS (3 equivs.) at the presence of 1 mol % of AIBN. Reaction mixtures were irradiated with microwaves for 10 min at 140 °C followed by work-up to afford the corresponding 3-bromoflavones **3** in excellent to quantitative yields. This methodology was found to work with a wide range of flavanones bearing electron-donating and electron-withdrawing substituents. As a control experiment, reactions were also performed under conditions of conventional heating in CCl_4; the results are listed in Table 3.

As shown in Table 3, it takes 24 hours to obtain 3-bromoflavones in moderate yields under conventional conditions. Moreover, prolonging the reaction time or adding excess brominating reagents under conventional conditions did not improve the yield because the flavones **2** formed during the reaction were very difficult to convert completely to the 3-bromoflavones **3**. Under microwave irradiation, by contrast, the solvent-free reaction was completed in 10 min and highly selective brominated products, 3-bromoflavones, were isolated in excellent to quantitative yields. It was previously reported that bromination of partial acetate esters of flavanones with NBS or Br_2/pyridine system in CCl_4 gave two A-ring brominated by-products,[8] namely 6,8-diflavanone esters and 6,8-dibromoflavone esters. However, we observed no such A-ring brominated by-products in spite of the fact that we detected dehydrogenated product flavones (0–9%).

Thus, by using microwave irradiation, we have developed an efficient synthesis of flavones under mild conditions by the bromination of flavanones. In addition, we explored the synthesis of 3-bromoflavones also starting from flavanones, by adjusting the molar ratio of NBS to flavanones. Microwave irradiation of 1 equiv. of flavanones **1** and 1 equiv. of NBS for 10 min at 100 °C produced the flavones **2** in good to excellent yields, and microwave irradiation of a solvent-free mixture of 1 equiv. of flavanones **1** and 3 equivs. of NBS at 140 °C for 10 min afforded the 3-bromoflavones **3** in excellent to quantitative yields.

In conclusion, we have presented the first report of a selective and fast transformation of flavanones with various substituents to the corresponding 3-bromoflavones and flavones by using NBS as a brominating reagent under microwave irradiation. This highly selective and efficient protocol involves the use of a cheap, stable, and safe reagent, and a simple work-up. Moreover, this protocol outperforms other currently available methods for the synthesis of 3-bromoflavones.

Experimental Section

Traditional Preparation of Flavones

NBS (1 mmol) and a catalytic amount of AIBN were added to a solution of flavanone **1** (1 mmol) in anhydrous CCl_4 (5 mL). The resulting solution was refluxed and monitored by TLC. After refluxing for 12 h, the reaction mixture was filtered. The filtrate was condensed under reduced pressure and the residue was chromatographed to give flavone **2** and a small amount of 3-bromoflavone **3**.

Preparation of Flavones 2 under Microwave Irradiation

NBS (1 mmol) and a catalytic amount of AIBN were added to a solution of flavanone **1** (1 mmol) in anhydrous CCl_4 (5 mL) in a microwave tube. The sealed tube was placed in a SmithsynthesizerTM and irradiated at 100 °C for 10 min. The resulting mixture was filtered. The filtrate was condensed under reduced pressure and the residue was chromatographed or recrystallized to give flavone **2**.

3′-Chloroflavone (2b): mp 109–110°; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81 (s, 1H), 7.43–7.48 (m, 2H), 7.51(d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.71–7.74 (m, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 8.25 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.0 (C-3), 118.0 (C-8), 123.7 (C-10), 124.3 (C-6′), 125.4 and 125.6 (C-6 or C-5), 126.2 (C-2′), 130.3 (C-5′), 131.4 (C-4′), 133.4 and 133.9 (C-1′ or C-7′), 135.1 (C-Cl), 156.0 (C-9), 161.5 (C-2), 178.2 (C=O); anal. calcd. for $C_{15}H_9ClO_2$: C 70.19, H 3.53; found: C 69.99, H 3.42.

3′-Bromoflavone (2d): mp 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80 (s, 1H), 7.40–7.45 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.72 (m, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 8.09 (s, 1H), 8.24 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.0 (C-3), 118.1 (C-8), 123.1 and 123.7 (C-10 or C-6′), 124.80 (C-6), 125.4 and 125.6 (C-2′ or C-5), 129.1 (C-5′), 130.5 (C-4′), 133.6 (C-1′), 134.0 and 134.4 (C-7 or C-3′), 156.0 (C-9), 161.6 (C-2), 178.2 (C=O); anal. calcd. for $C_{15}H_9BrO_2$: C 60.11, H 2.90; found: C 59.83, H 3.01.

7-Methoxy-4′-chloroflavone (2h): mp 159–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.99 (s, 3H), 6.78 (s, 1H), 7.00–7.10 (m, 2H), 7.45–7.90 (m, 4H), 8.18 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8 (CH_3-O), 99.8 (C-8), 107.7 (C-3), 114.4 (C-6), 117.5 (C-10), 126.8 (C-5), 129.0 (C-2′ and C-6′), 131.2 and 131.6 [(C-3′ and C-5′) or C-1′), 134.7 (C-4′), 157.9 (C-9), 162.8 (C-2), 164.4 (C-7), 178.8 (C=O); anal. calcd. for $C_{16}H_{11}ClO_3$: C 67.03, H 3.87; found: C 67.34, H 3.56.

Traditional Preparation of 3-Bromoflavones 3

NBS (3 mmol) and a catalytic amount of AIBN were added to a solution of flavanone **1** (1 mmol) in anhydrous CCl_4 (5 mL). The resulting solution was refluxed and monitored by TLC. After refluxing for 24 h, the reaction mixture was filtered. The filtrate was condensed under reduced pressure and the residue was chromatographed to give 3-bromoflavone **3** and a small amount of flavone **2**.

Preparation of 3-Bromoflavones 3 under Solvent-Free Microwave Irradiation

NBS powder (3 mmol), a catalytic amount of AIBN and flavanone **1** powder (1 mmol) were mixed and added into a microwave tube. The sealed tube was placed in a SmithsynthesizerTM and irradiated at 140 °C for 10 min. The resulting mixture was chromatographed or recrystallized to give 3-bromoflavone **3**.

3-Bromo-3′-chloroflavone (3b): mp 173–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.55 (m, 4H), 7.72–7.78 (m, 2H), 7.83 (t, *J* = 1.6 Hz, 1H), 8.29 (dd, *J* = 8 Hz, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.6 (C-3), 117.9 (C-8), 121.7(C-10), 125.9 and 126.6 (C-5 or C-6′), 127.6 (C-6), 129.3 and 129.7 (C-1′ or C-2′), 131.2 (C-5′), 132.3 (C-4′), 133.8 and 134.4 (C-7 or C-3′), 155.5 (C-9), 160.4 (C-2), 172.9 (C=O); EI-MS: *m/z* = 336 (M^+), 334 [$(M-2)^+$]; anal. calcd. for $C_{15}H_8BrClO_2$: C 53.69, H, 2.40; found: C 53.86, H 2.44.

3,3′-Dibromoflavone (3d): mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.53 (m, 4H), 7.68–7.83 (m, 2H), 7.99 (t, *J* = 1.8 Hz, 1H), 8.31 (dd, *J* = 8.2 Hz, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109. 7 (C-3), 117.9 (C-8), 121.7 and 122.3 (C-5 or C-10), 125.8 and 126.4 (C-6′ or C-6), 128.0 (C-2′), 129.9 (C-1′), 131.9 and 132.1 (C-4′ or C-5′), 134.1 and 134.4 (C-3′ or C-7), 155.6 (C-9), 160.3 (C-10), 172.9 (C=O); EI-MS: *m/z* = 382 [$(M+2)^+$], 380 (M^+), 378 [$(M-2)^+$]; anal. calcd. for $C_{15}H_8Br_2O_2$: C 47.41, H 2.12; found: C 47.61, H 2.10.

3-Bromo-4′-chloro-7-methoxyflavone (3h): mp 188–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3H), 6.85 (d, *J* = 2.0 Hz, 1H), 7.03 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 7.50 (dd, *J* = 6.8 Hz, 2 Hz, 2H), 7.80 (dd, *J* = 6.6 Hz, 1.8 Hz, 2H), 8.19 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9(CH_3-O), 99.8 (C-8), 109.5 (C-3), 115.3 and 115.5 (C-6 or C-10), 127.9 (C-5), 128.6 (C-2′ and C-6′), 130.6 (C-3′ and C-5′), 131.2 (C-1′), 137.2 (C-4′), 157.3 (C-9), 160.2 (C-2), 164.5 (C-7), 172.2 (C=O); EI-MS: *m/z* = 366 (M^+), 364 [$(M-2)^+$]; anal. calcd. for $C_{16}H_{10}BrClO_3$: C 52.56, H 2.76; found: C 52.36, H 2.59.

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