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PII: S0040-4039(19)31310-3
DOI: https://doi.org/10.1016/j.tetlet.2019.151511
Reference: TETL 151511

To appear in: *Tetrahedron Letters*

Received Date: 9 November 2019
Revised Date: 5 December 2019
Accepted Date: 6 December 2019

Please cite this article as: Peng, T., Wang, G., Zhang, S., Sun, Y., Liu, S., Wang, L., One-pot synthesis of 3-haloflavones from flavones using Oxone® and potassium halide as a halogenation reagent, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151511

Graphical Abstract

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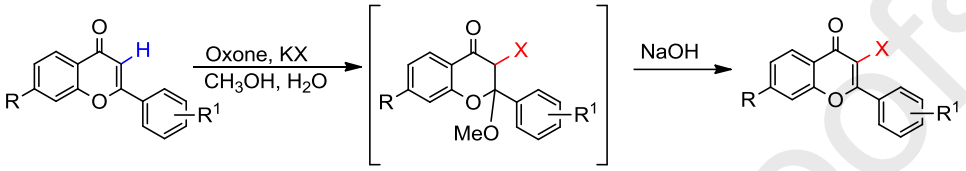

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One-pot synthesis of 3-haloflavones from flavones using Oxone® and potassium halide as a halogenation reagent

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
3-Haloflavones
One-pot synthesis
Halogenation
Flavones

ABSTRACT

A two-step, one-pot method has been developed for the synthesis of 3-haloflavones from the corresponding flavones. The method uses Oxone® and potassium halide to produce the active molecular halogen *in situ*. The solvent (methanol) then participates in the reaction to afford the 2-methoxy-3-haloflavanone derivative. After adding sodium hydroxide, the corresponding 3-haloflavone product is obtained in good to excellent yields. This method provides a convenient synthesis of 3-chloro, 3-bromo and 3-iodo flavones from the same flavone starting material.

Introduction

Flavones, as micronutrients in our diet, can be found in many vegetables and fruits.[1] The bioactivities displayed by flavones are wide ranging and include anti-inflammatory,[2] antioxidant,[3] anticancer,[4] and other activities.[5] The flavone structure is also an important building block for the synthesis of bioactive compounds.[6] In order to alter and improve the bioactivity of flavones, significant research effort has been devoted towards modifying their structures.[7] Among these modifications, 3-haloflavones are useful intermediates for the synthesis of C_3-substituted flavones and C_3-linked bioflavonoids.[8]

3-Haloflavones can be synthesized using indirect or direct methods. Indirect methods prepare 3-haloflavones *via* cyclization of their precursors, which are halogenated before or at the same time as formation of the target flavone.[9] Direct methods prepare 3-haloflavones from their corresponding flavones *via* halogenation. Considering that flavones can be acquired conveniently using organic synthesis or from natural sources, the use of direct methods to prepare 3-haloflavones has been extensively studied. Among the direct methods reported to date, most of the reported research work has focused on the synthesis of 3-iodoflavones, which are prepared *via* iodinating flavones using I_2/CAN,[10] LDA/I_2,[11] or I_2/DMSO.[12] There are some reports on the synthesis of 3-bromoflavones and 3-chloroflavones from flavones using 2,4,4,6-tetrabromo-2,5-cyclohexadienone,[13] Bu_4NBr/PhI$(OAc)_2$,[14] pyridinium bromide perbromide,[15] and NCS[16] as bromination and chlorination reagents. However, most of these methods are of limited use due to the requirement of toxic or unstable reagents, tedious synthetic procedures, and low yields. An interesting study on the preparation of 3-bromoflavones and 3-chloroflavones *via* the reaction of the corresponding flavones with PhI$(OAc)_2$/TMSBr or PhI$(OAc)_2$/TMSCl has been reported.[17] This method is very attractive to medicinal chemists because it allows the synthesis of 3-bromoflavones and 3-chloroflavones from the same starting materials under similar reaction conditions. However, this method is of limited use because only four compounds were synthesized and 3-iodoflavones were not obtained when using PhI$(OAc)_2$/TMSI as the iodinating reagent. Furthermore, the quantity of TMSBr or TMSCl (3.0 equiv.) and PhI$(OAc)_2$ (1.5 equiv.) used in the method, render it economically unattractive.

Oxone® is a widely used reagent in organic synthesis and exhibits many useful properties such as being easy to handle, water soluble, non-toxic, stable, and inexpensive.[18] There are numerous reports on the efficient halogenation of aromatic compounds using binary systems consisting of Oxone®/KX (X = Cl, Br, and I). In continuation of our interest in the halogenation of organic compounds using Oxone®/KX, we report a two-step, one-pot method for transforming flavones into 3-haloflavones using Oxone®/KX as the halogenation reagent.

Results and Discussion

Initially, 4'-methoxyflavone (**1a**) was chosen as the model substrate to explore the synthesis of 3-iodoflavones from flavones using Oxone®/KI as an iodinating reagent (Scheme 1). The reaction conditions were as follows: flavone **1a** (0.5 mmol), KI (0.5 mmol) and Oxone® (0.5 mmol) were stirred in methanol (12 mL) at room temperature for 16 h. Unfortunately, the desired product **3a** was not obtained. The structure of the product was

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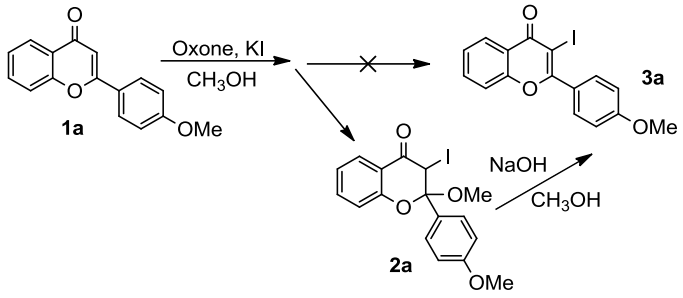
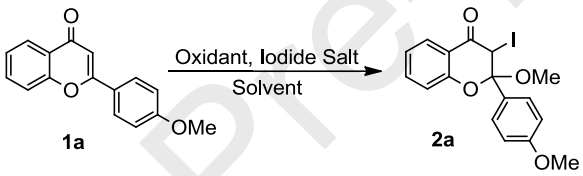
determined to be 2-methoxy-3-iodo-4'-methoxyflavanone (**2a**) using ^{1}H-NMR, ^{13}C-NMR, HMQC, and HMBC (see ESI for spectra). We found that **2a** could be almost quantitatively converted into 3-iodo-4'-methoxyflavone (**3a**) within a short time when treated with a catalytic amount of NaOH in methanol. Subsequently, we developed a two-step method for the synthesis of **3a** from **1a** (Scheme 1).



Scheme 1. Two-step synthesis of 3-iodo-4'-methoxyflavone (**2a**).

The synthesis of 3-iodoflavones from flavones can be accomplished in one-pot because the two reactions steps use the same solvent (CH_3OH). To develop our methodology, the reaction conditions used to prepare **2a** were initially optimized. The results of the optimization experiments are summarized in Table 1. The yield of **2a** was 53% using 1.0 equiv. of Oxone® and KI in CH_3OH (Entry 1). However, no reaction took place when using CH_3CN or THF as the solvent under the same reaction conditions (Entries 2 and 3). We assumed the methoxy group in **2a** originates from the reaction solvent (CH_3OH). An isotope labelling experiment was conducted using CD_3OD as the reaction solvent and the results confirmed our assumption (see ESI for experimental details). In order to increase the solubility of the inorganic salts used in the reaction, an aqueous solution of methanol was used and we were pleased to find the yield of **2a** increased (Entry 4). The yield of **2a** changed when the quantity of oxone and KI was increased from 1.0 to 2.0 equiv. (Entries 4–7). This optimization indicated that 1.2 equiv. of Oxone® and KI gave the best results (Entry 5). Increasing the proportion of water in the solvent increases the solubility of the inorganic salts, but also decreases the solubility of the reaction substrates. The optimal ratio of methanol to water was determined as 12:0.2 (v/v), which gave **2a** in 92% yield (Entry 8). Under the optimal reaction conditions, the yield of **2a** decreased slightly when using other iodides, such as NH_4I and *n*-Bu_4I (Entries 9 and 10). We decided to use KI as the optimal iodide salt due to its low cost.

Table 1.
Optimization of the reaction conditions used to prepare **2a**.[a]



Entry	Oxone®	Iodide salt	Solvent	Yield **2a** (%) [b]
1	1.0 equiv.	1.0 equiv. KI	CH_3OH (12 mL)	53
2	1.0 equiv.	1.0 equiv. KI	CH_3CN (12 mL)	–
3	1.0 equiv.	1.0 equiv. KI	THF (12 mL)	–
4	1.0 equiv.	1.0 equiv. KI	CH_3OH/H_2O (12 mL/0.5 mL)	74
5	1.2 equiv.	1.2 equiv. KI	CH_3OH/H_2O (12 mL/0.5 mL)	81
6	1.5 equiv.	1.5 equiv. KI	CH_3OH/H_2O (12 mL/0.5 mL)	76
7	2.0 equiv.	2.0 equiv. KI	CH_3OH/H_2O (12 mL/0.5 mL)	69
8	1.2 equiv.	1.2 equiv. KI	CH_3OH/H_2O (12 mL/0.2 mL)	92
9	1.2 equiv.	1.2 equiv. NH_4I	CH_3OH/H_2O (12 mL/0.2 mL)	88
10	1.2 equiv.	1.2 equiv. *n*-Bu_4I	CH_3OH/H_2O (12 mL/0.2 mL)	89

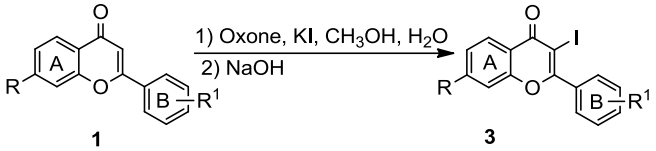
[a] Reagents and conditions: flavone **1a** (0.5 mmol), iodide salt and Oxone® were suspended in the reaction solvent and the resulting mixture was stirred at room temperature. After reaction completion, the reaction mixture was quenched with water. The product was purified by SiO_2 column chromatography.
[b] Isolated yield based on **1a**.

With the optimized reaction conditions in hand, we explored the synthesis of **3a** from **1a** in one-pot. When **1a** was not detected in the reaction mixture by TLC, NaOH was added to the reaction. Considering that Oxone® is a triple acid salt ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), 5.0 equiv. of NaOH was added to the reaction mixture to counteract the acid salts. As expected, **3a** was obtained in 87% yield (Table 2, entry 1). To extend our study, the optimized conditions were applied to other flavones and the results are summarized in Table 2. A wide range of substituted flavones were transformed into their corresponding 3-iodoflavones in moderate to high yields. Flavones containing a *para*-methoxy substituent on ring B performed better than the *meta*- and *ortho*-substituted substrates (Entries 1–3 and 7–9). Substrates bearing an *ortho*-substituent on ring B gave the desired product in low yields, which may be attributed to steric hindrance (Entries 2 and 8). Among the substrates bearing a *para*-substituent on ring B, electron-donating groups afforded the desired product in high yields (Entries 1, 4, and 7), while electron-withdrawing groups gave relatively low yields (Entries 5, 6, and 10). Flavones containing a phenolic hydroxyl group gave a complex mixture of products under these reaction conditions, but the reaction was improved when the hydroxyl group was protected using a benzyl group (Entry 4). Substitution on ring A did not significantly affect the yield. Surprisingly, **1k** and **1l**, in which ring B contains three electron-donating groups, did not give the aromatic iodination product. The halogenation of aromatic rings is an aromatic electrophilic substitution reaction and the higher the electron density in the aromatic ring, the easier

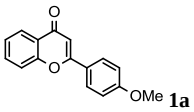
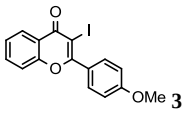
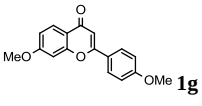
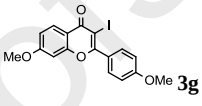
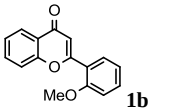
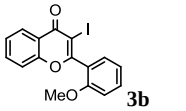
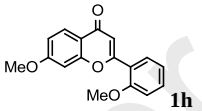
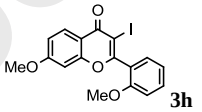
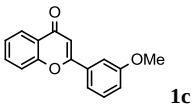
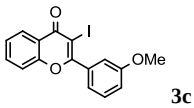
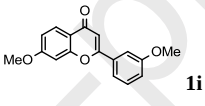
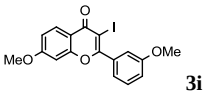
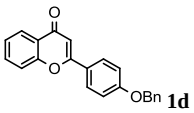
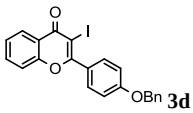
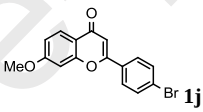
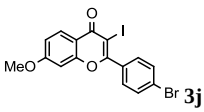
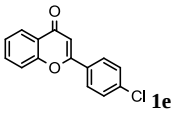
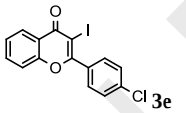
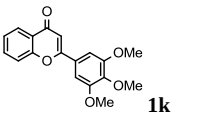
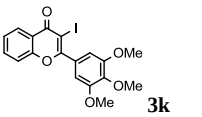
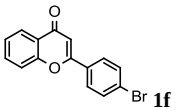
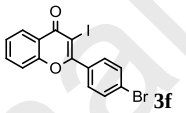
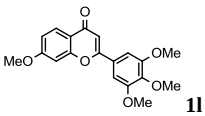
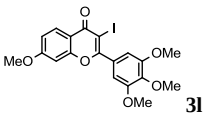
the ity ring can be reflected by the chemical shifts of the aromatic protons observed in the ^{1}H-NMR spectrum. From the reported ^{1}H-NMR data, the aromatic proton signals in ring B of **1k** and **1l** are observed at δ = 7.15 and 7.12, respectively.[19] As the proton in ring B of **1k** and **1l** is not much higher than that of benzene. This may explain why **1k** and **1l** did not give the aromatic iodination products.

Table 2.

One-pot synthesis of 3-iodoflavone derivatives.[a]



1 **3**

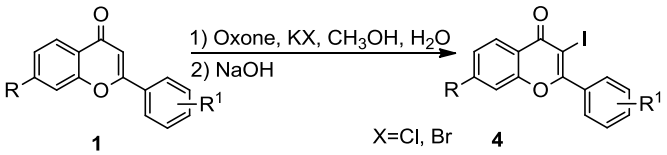
Entry	Substrate **1**	Time	Product **3**	Yield (%)[b]	Entry	Substrate **1**	Time	Product **3**	Yield (%)[b]
1	 **1a**	14 h	 **3**	87	7	 **1g**	14 h	 **3g**	83
2	 **1b**	15 h	 **3b**	79	8	 **1h**	22 h	 **3h**	77
3	 **1c**	10 h	 **3c**	82	9	 **1i**	14 h	 **3i**	81
4	 **1d**	16 h	 **3d**	91	10	 **1j**	14 h	 **3j**	73
5	 **1e**	18 h	 **3e**	85	11	 **1k**	10 h	 **3k**	77
6	 **1f**	9 h	 **3f**	84	12	 **1l**	17 h	 **3l**	74

[a] Reagents and conditions: flavone **1** (0.5 mmol), KI (0.6 mmol) and Oxone® (0.6 mmol) were suspended in CH_3OH (12 mL) and H_2O (0.2 mL). The resulting mixture was stirred at room temperature until the substrate disappeared by TLC. NaOH (2.5 mmol) was added to the reaction mixture and after 10 min, the reaction was quenched with water. The product was purified by SiO_2 column chromatography. [b] Isolated yield based on **1**.

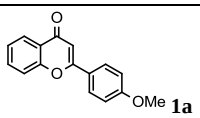
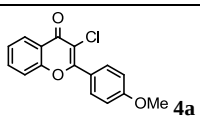
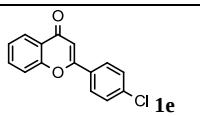
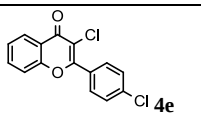
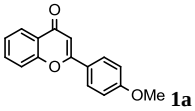
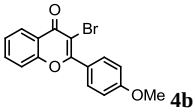
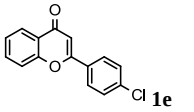
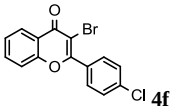
Encouraged by the synthesis of 3-iodoflavones, we decided to use this method to prepare a variety of 3-chloroflavone and 3-bromoflavone derivatives by replacing KI with KCl and KBr, respectively, and the results summarized in Table 3. Gratifyingly, the 3-chloroflavone or 3-bromoflavone derivatives were obtained in improved yields with shorter reaction times.

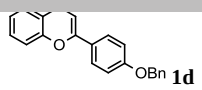
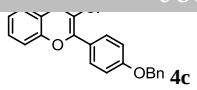
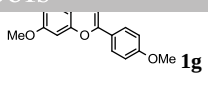
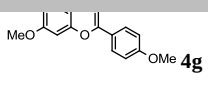
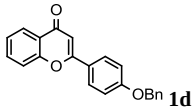
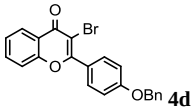
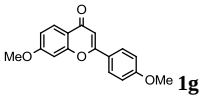
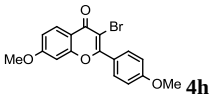
Table 3.

One-pot synthesis of 3-chloroflavone and 3-bromoflavone derivatives. [a]

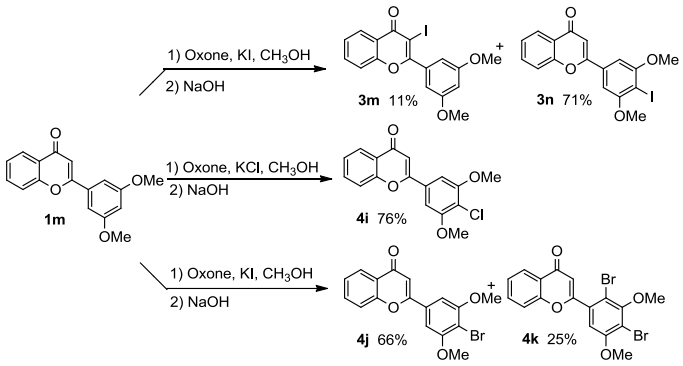


1 **4**

Entry	Substrate **1**	Time	Product **4**	Yield (%)[b]	Entry	Substrate **1**	Time	Product **4**	Yield (%)[b]
1	 **1a**	12 h	 **4a**	89	5	 **1e**	14 h	 **4e**	89
2	 **1a**	3 h	 **4b**	86	6	 **1e**	7 h	 **4f**	86

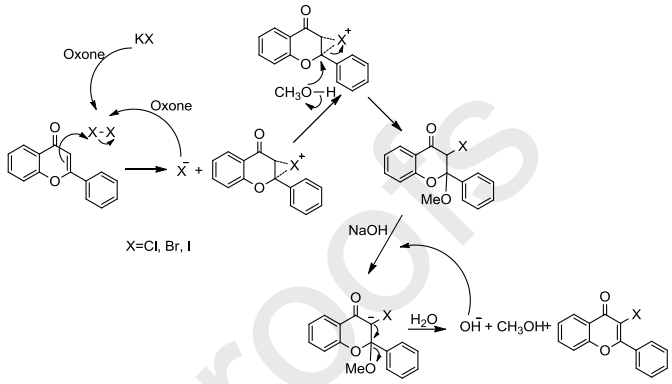
3	 **1d**	9 h	 **4c**	82	7	 **1g**	11 h	 **4g**	88
4	 **1d**	8 h	 **4d**	84	8	 **1g**	3 h	 **4h**	93

[a] Reagents and conditions: flavone **1** (0.5 mmol), KX (0.6 mmol, KCl=45 mg, KBr=71 mg) and Oxone® (0.6 mmol) were suspended in CH_3OH (12 mL) and H_2O (0.2 mL). The resulting mixture was stirred at room temperature until the substrate disappeared by TLC. NaOH (2.5 mmol) was added to the reaction mixture and after 10 min, the reaction was quenched with water. The product was purified by SiO_2 column chromatography. [b] Isolated yield based on **1**.



Scheme 2. Halogenation of 3',5'-dimethoxyflavone.

Oxone® and halogenated salts are reagents commonly used in aryl halogenation reactions.[20] Although no aromatic halogenation compounds were observed in the above examples (Table 2 and Table 3), there is likely to be a competitive halogenation reaction between the C_3-position and the aromatic ring when the aromatic ring contains an appropriate activating group. We chose 3',5'-dimethoxyflavone (**1m**) to demonstrate this competitive reaction, as shown in Scheme 2. When using Oxone® and KI as the iodinating reagent, the yield of 3-iodoflavone **3m** was only 11% and the aromatic iodination compound **3n** became the main product. In the chlorination reaction, 4'-chloroflavone **4i** was isolated in 76% yield. Two aromatic bromination products, **4j** and **4k**, were obtained in the bromination reaction in 66% and 25% yield, respectively. No 3-chloroflavone or 3-bromoflavone products were formed in these two reactions. The presence of the 3',5'- dimethoxy groups in **1m** allow the halogenation reaction to take place at the 4'-position, instead of the C_3-position. The differences in the halogenation products of **1m** can be attributed to the atomic radius of chlorine, bromine and iodine. The iodine atom faces greater steric hindrance at the 4'-position because it has the largest atomic radius among the three halogens studied. This results in the formation of a small amount of 3-iodoflavone **3m**. Therefore, we can conclude that the aromatic halogenation compound may become the main product under these reaction conditions when there is more than one activating group (electron-donating group) at appropriate positions in the flavone starting material.



Scheme 3. Proposed reaction mechanism.

Finally, a reaction mechanism for the synthesis of 3-haloflavones has been proposed based on our results, as shown in Scheme 3. Oxone® reacts with the potassium halide to generate the active molecular halogen. The halonium intermediate is formed *via* addition of the active molecular halogen to the C=C bond in the flavone starting material. Then, nucleophilic attack by methanol on the halonium intermediate gives 2-methoxy-3-haloflavanone as an isolable intermediate. Deprotonation occurs at the C_3-position after adding NaOH to the reaction mixture. Consequently, the 3-haloflavone product is generated *via* elimination of the methoxy group.

Conclusion

In conclusion, we have developed a mild and convenient one-pot method for the synthesis of 3-haloflavones from the corresponding flavones. The protocol uses readily available and inexpensive Oxone® and potassium halide to produce the active molecular halogen *in situ*. The solvent (methanol) then participates in the reaction to afford the 2-methoxy-3-haloflavanone derivative. After adding NaOH to the reaction mixture, the 3-haloflavone product is obtained in good to excellent yields. The method provides a convenient and facile synthesis of 3-chloro, 3-bromo and 3-iodo flavones from the same flavone starting material.

Acknowledgments

This work was supported financially by the National Natural Science Foundation of China (21272273 and 81273431), which is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/

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Highlights

- 3-Haloflavones were synthesized from the corresponding flavones.
- This method use Oxone® and potassium halide as a halogenation reagent.
- 3-Chloro, 3-bromo and 3-iodo flavones can be conveniently synthesized.