New Synthesis of 3-Bromoflavones via Bromination of 1-(2-Hydroxyphenyl)-3-arylpropane-1,3-dione by $CuBr_2$, and Conversion into 3-Aminoflavones

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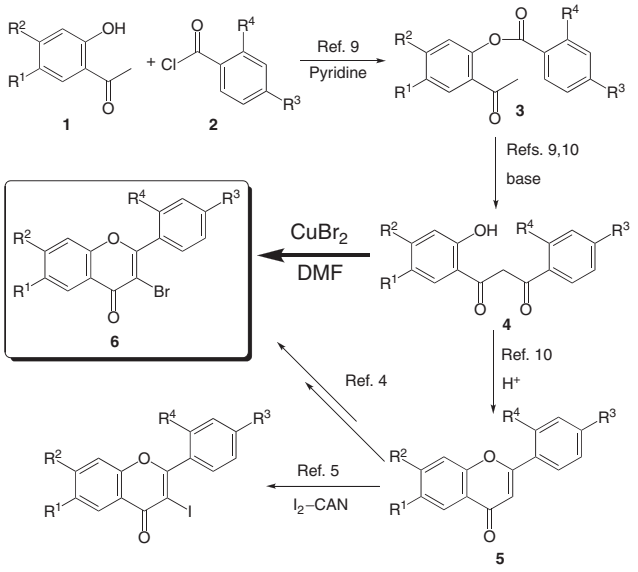
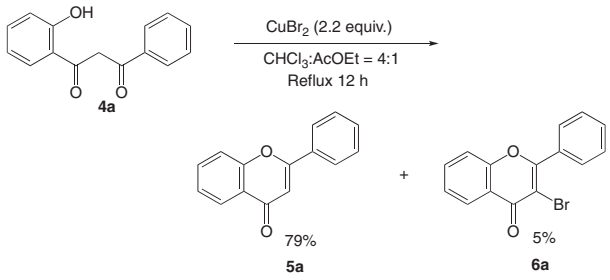
(Received December 8, 2006; CL-061443; E-mail: miyakeh@kobe-u.ac.jp)

A new synthesis of 3-bromoflavones from 1-(2-hydroxyphenyl)-3-arylpropane-1,3-dione using $CuBr_2$ is described. The usefulness of 3-bromoflavone as a precursor of 3-aminoflavone is also described.

There has been increasing interest in the biological activities of 3-substituted flavones,[1] and 3-haloflavones are useful precursors for the synthesis of 3-substituted flavones.[2] Our recent report,[3] which described a direct conversion from 3-tosyloxyflavones to 3-aminoflavones, suggests that the 3-haloflavones can also be used as precursors of 3-aminoflavones. The synthesis of 3-haloflavones can be accomplished by many methods. For example, multi-step bromination of flavones,[4] iodination of flavones using I_2–CAN,[5] microwave-assisted bromination of flavanones by NBS,[6] cyclization of 2-hydroxychalcone dibromide,[7] and bromination of 1,3-diketones **4** followed by cyclization[8] have been reported. Some of these methods begin with flavones, which must be prepared beforehand. The most popular method for preparing flavones is based on the one shown in Scheme 1. It contains the benzoylation of 2-hydroxyacetophenone **1**, followed by base-mediated isomerization to 1,3-diketone **4** (Baker–Venkataraman rearrangement).[9] Acid-catalyzed cyclization of **4** yields flavone **5**.[10] Apparently, a direct conversion from **4** to 3-haloflavone is more effective than a conversion from **5** (Scheme 1). The methods, starting from **4** using HBr–H_2O_2[8a] or Br_2,[8b–8d] have been reported. However, these compounds require careful handling, and they may cause an undesired reaction such as bromination or oxidation on the aromatic ring.



Scheme 1.

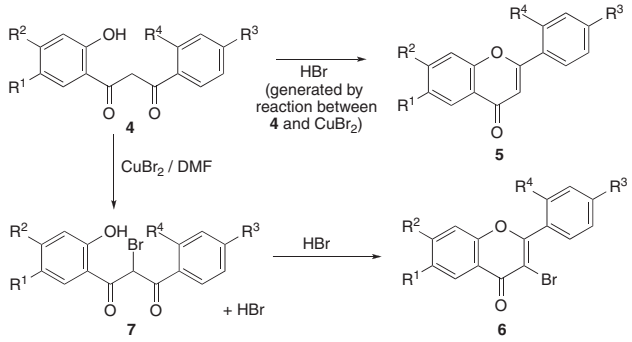


Scheme 2.

In this paper, we report a facile method for the synthesis of 3-bromoflavone **6** by one-pot reaction of 1,3-diketone **4** with readily available $CuBr_2$. Some examples of the conversion of 3-bromoflavones into 3-aminoflavones are also described.

Copper(II) bromide was useful as brominating reagent and was often used as a suspension in $CHCl_3$–AcOEt for bromination of ketones. The reaction with aromatic ketones proceeded chemoselectively to give α-bromoketones without affecting the aromatic rings.[11] However, when **4a** was heated with $CuBr_2$ in $CHCl_3$–AcOEt, 3-bromoflavone **6a** was obtained in only a 5% yield, and flavone **5a** was obtained as a major product in a 79% yield (Scheme 2).

In order to suppress the undesired production of **5a**, we used DMF as a solvent. Results are summarized in Table 1.[12] In most cases, the reaction proceeded smoothly at 130 °C to give **6** as a major product. When 3 equiv. of $CuBr_2$ were used for the conversion from **4a**, a considerable amount of **5a** was obtained. However, when 4 equiv. of $CuBr_2$ were used at 130 °C, **5a** was not obtained, whereas small (or often considerable) amounts of



Scheme 3.

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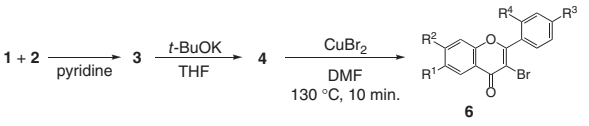
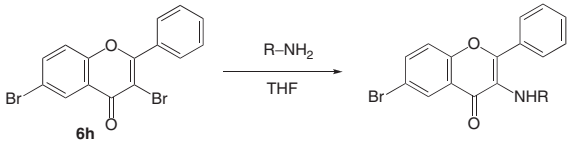
Table 1. Synthesis of 3-bromoflavone **6** from **1** and **2**



R^1	R^2	R^3	R^4	Yield of **3**/%[a]	Yield of **4**/%[a]	$CuBr_2$ (equiv.)	Yield of **6**/%[a]
H	H	H	H	**3a** 60	**4a** 60	2.2	**6a** 53(30)[b]
						3.0	54(22)[b]
						4.0	68
Me	H	H	H	**3b** 91	**4b** 54	4.0	**6b** 70
Cl	H	H	H	**3c** 89	**4c** 53	4.0	**6c** 75
H	MeO	H	H	**3d** 96	**4d** 68	4.0[c]	**6d** 49
Cl	H	*t*-Bu	H	**3e** 91	**4e** 77	4.0	**6e** 57
Me	H	H	Cl	**3f** 99	**4f** 85	4.0	**6f** 55
Cl	H	F	H	**3g** 82	**4g** 84	4.0	**6g** 50
Br	H	H	H	**3h** 96	**4h** 84	4.0	**6h** 82
Br	H	H	Cl	**3i** 91	**4i** 78	4.0	**6i** 66

[a]Isolated yield. [b]Yield of **5** is in parentheses. [c]Reaction conditions: 110 °C, 25 min.



Entry 1	R = Et (70% aqueous solution)	r. t., 12 h	**8a** 90%
2	R = *n*-Pr	r. t., 12 h	**8b** 98%
3	R = *n*-Bu	r. t., 3.5 h	**8c** 88%
4	R = *c*-Hex	60 °C, 6 h	**8d** 85%
5	R = H (28% aqueous solution)	r. t., 12 h	**8e** 57%
6	R = H (28% aqueous solution, DMF was used as solvent)	50 °C, 15 h	**8e** 86%

Scheme 4.

unidentified products were obtained.

The effectiveness of DMF can be explained as follows (Scheme 3). When **4** was treated with $CuBr_2$, bromination of **4** proceeded smoothly to give **7** and HBr, and the latter catalyzed the cyclization of **7** to give **5**. However, HBr also catalyzed the cyclization of **4** to give the undesired product **5**. When a solvent other than DMF was used, acid (HBr)-catalyzed cyclization proceeded more smoothly than the bromination of **4**, and in that case, **5** was obtained as a major product. On the other hand, because of its basisity, DMF trapped H^+ to some extent and moderately suppressed the acid-catalyzed cyclization.

The ammonia and primary amines shown in Scheme 4 reacted with **6h**, which was prepared by the procedures described above, to give 3-aminoflavones **8** in a good yield.[13] In the cases of ethylamine (Entry 1) and ammonia (Entries 5 and 6), an aqueous solution of amines can be used. Using DMF as a solvent for the reaction with aqueous NH_3 is effective for improving the yield of **8**. The reaction of aqueous NH_3 with **6h** gave **8e** in an 86% yield (Entry 6), whereas the corresponding reaction in THF gave **8e** in only a 57% yield (Entry 5). Probably because of its poor nucleophilicity, aniline did not react with **6h** even under reflux conditions for 15 h.

In conclusion, the reaction of **4** with $CuBr_2$ in DMF is an effective method for the synthesis of **6**. Furthermore, **6** is as good a precursor of **8** as 3-tosyloxy- or 3-mesyloxyflavone.[3]

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12 Typical procedures are as follows.
Synthesis of **3b**. Benzoyl chloride (4.5 g, 32 mmol) was added to a pyridine (10 mL) solution of 5-methyl-2-hydroxyacetophenone (4.5 g, 30 mmol). The mixture was heated at 70 °C for 10 min. The mixture was poured into cool 3 M HCl (40 mL) and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was recrystallized from methanol to give **3b** (6.9 g, 27 mmol) in 91% yield.
Synthesis of **4b**. Potassium *t*-butoxide (90% purity, 3.7 g, 30 mmol) was added to a THF (30 mL) solution of **3b** (6.9 g, 27 mmol). The mixture was stirred at r.t. for 10 min. The mixture was poured into cool 3 M HCl (30 mL) and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was recrystallized from methanol to give **4b** (3.7 g, 15 mmol) in 54% yield.
Synthesis of **6b**. A DMF (6 mL) solution of **4b** (0.76 g, 3.0 mmol) was heated to 130 °C. Copper(II) bromide (2.68 g, 12 mmol) was added to the solution and stirred for 10 min. The mixture was poured into water and extracted with ethyl acetate. After the usual workup, the crude product was purified by column chromatography on silica gel to give **6b** (0.66 g, 2.1 mmol) in 70% yield.

13 Typical procedures are as follows.
Synthesis of **8c**. A THF (1.5 mL) solution of **6h** (0.114 g, 0.30 mmol) and butylamine (0.55 g, 0.75 mmol) was stirred at r.t. for 3.5 h. The mixture was poured into water (10 mL) and extracted with ethyl acetate. After the usual workup, the crude product was recrystallized from $CHCl_3$ to give **8c** (0.098 g, 0.26 mmol) in 88% yield. In the cases of **8a** and **8e** (Entries 1, 5, and 6), a large excess (10–20 equiv.) of amines was used.

Published on the web (Advance View) March 10, 2007; doi:10.1246/cl.2007.522