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Regioselective 6-iodination of 5,7-dioxygenated flavones by benzyltrimethylammonium dichloroiodate

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Abstract—The iodination of 5,7-dioxygenated flavones with 1 equiv of benzyltrimethylammonium dichloroiodate (BTMA·ICl_2) in the system CH_2Cl_2–MeOH–$CaCO_3$ at room temperature is presented in this note. Flavones with a free phenol group at C5 and an alkoxy or a peracylglycosyloxy at C7 lead to the 6-iodoflavones with a good regioselectivity (ratio 6-iodination/8-iodination about 9).
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1. Introduction

Biflavonoids are a group of naturally occurring compounds endowed with a variety of biological activities (antimicrobial, cytotoxic, antiinflammatory and others).[1,2] Among them, biflavones with units connected via at least one 6-position include some interesting structures such as robustaflavone **1**,[3] an inhibitor of hepatitis B virus (HBV)[4,5] replication and 6,6″-biapigenin hexamethylether **2**, an antituberculosis agent.[6,7] In 1998, a total synthesis of robustaflavone was performed through, as a key step, a Suzuki coupling of the 6- iodoapigenin derivative **4** with the 3′-boronate **5**.[5] Compound **4** was prepared from **3** ((a) BBr_3; (b) I_2/TlOAc in CH_2Cl_2, 73%; (c) Me_2SO_4) by exploiting the *ortho*-directing capabilities of thallium(I) salts in the iodination of phenols.[8] Until now, this straightforward method remained the only one which provided 6-iodo compounds in good yield since iodination (and generally electrophilic substitutions) of 5,7-dioxygenated flavones are known to occur rather at C8.[9–11] However, this easy reaction requires TlOAc, a highly toxic reagent, which accounts for the search of an alternative iodination method. This paper relates to a new regioselective 6-iodination of 5,7-dioxygenated flavones by the use of benzyltrimethylammonium dichloroiodate (BTMA·ICl_2), a commercially available, stable, crystallized and easy-handled reagent known to iodinate phenols under mild conditions.[12]

2. General procedure (from Kajigaeshi et al.)[12]

A mixture of flavone (1 equiv), BTMA·ICl_2 (1 equiv) and $CaCO_3$ (7 equiv) in CH_2Cl_2–MeOH 5:2 was stirred at room temperature until completion of the reaction (4–12 h). The reaction mixture was taken up in water and extracted at pH 6 with CH_2Cl_2 or CH_2Cl_2–MeOH (for 7-hydroxyflavones). Standard work-up of the organic layer provided a dried residue which was purified by flash chromatography on silica gel or crystallized (MeOH or EtOH). Characterization and purity of all iodo compounds followed from MS, homo- and heteronuclear NMR and microanalysis.

As iodination by BTMA·ICl_2 requires at least one free phenol, reactions were performed with 5-hydroxyflavones bearing at C7 various oxygenated groups (hydroxy, acetoxy, alkoxy, glycosyloxy).

2.1. Iodination of 5,7-dihydroxyflavones

Reaction of diosmetin **6** with 1 equiv of BTMA·ICl_2 provided according to TLC four compounds including the starting flavone. A second equivalent of BTMA·ICl_2 simplified the mixture, which led mainly to 6,8-diiododiosmetin **7** (54% after crystallization from EtOH;

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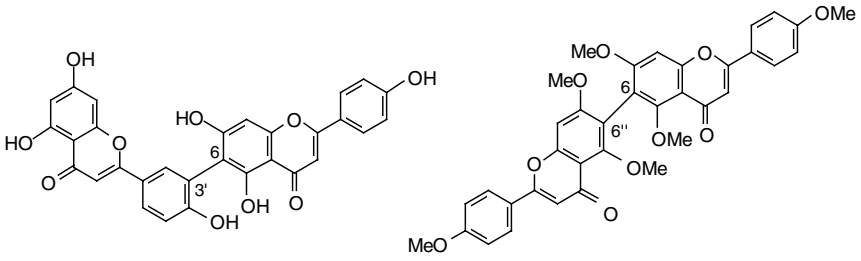


1 2

3 R = H
4 R = I

5

EIMS m/z 552 M^+; mp 249–251 °C). Similarly, acacetin **8** afforded 6,8-diodoacacetin **9** (EIMS m/z 536 M^+; mp 253–255 °C). It is noteworthy that the free phenol group at the 3′-position in **6** does not lead to iodination of the B ring.

2.2. Iodination of 7-acetoxyflavones

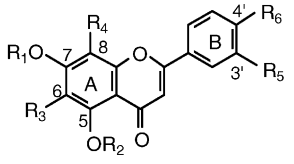
As compounds **6** and **8**, 7,3′-diacetyldiosmetin **10** was not iodinated in a regioselective manner since reaction with 1 equiv of BTMA·ICl_2 gave according to TLC a mixture of compounds including unreacted **10**. As expected, 5,7,3′-triacetyldiosmetin **11** with no more free phenol did not provide any compound under the same conditions.

2.3. Iodination of 5-hydroxy-7-alkoxyflavones

When the reaction was accomplished with 7,3′-dimethyldiosmetin **12**, BTMA·ICl_2 (1 equiv) gave quantitatively a mixture of two products in a 91/9 ratio [easily inferred from ^{1}H NMR spectrum by comparing integration of signals of the phenol proton at 13.7 (major) and 12.85 ppm (minor)]. The compounds had very close R_f in TLC (silica gel, CH_2Cl_2–MeOH 99.5:0.5) but the major one was isolated in good yield (73%) as pure 7,3′-dimethyl-6-iododiosmetin **13** by crystallization from MeOH (EIMS m/z 454 M^+; mp 227–230 °C). The iodo substitution at the 6-position was proved by comparative NMR experiments (NOESY and HMBC) on **12** and **13**. This conclusion was based on: (a) the loss for **13** of the Overhauser effect observed between the phenol proton and H6 for **12**; (b) the strong shielding by the iodine of the signal of C6 at 69.5 ppm for **13** (97.8 ppm for **12**), In the same manner, iodination of 7,4′-dimethylapigenin **14** afforded 7,4′-dimethyl-6-iodo-apigenin **15** in the same good yield (mp 227–229 °C; lit.[5] mp 227–228 °C). The 6-iodo substitution was unambiguously confirmed by methylation by phase-transfer catalysis of **15** into 6-iodo-trimethylapigenin **4** (mp 204–205 °C; lit.[5] mp 202–204 °C for 6-iodo-trimethylapigenin, lit.[13] mp 238 °C for 8-iodo-trimethylapigenin). Lastly, starting from 7-benzyldiosmetin **16** or 7,3′-dibenzyldiosmetin **17** allowed isolation after crystallization (77%) and identification (as for **13**) of the corresponding 6-iodo derivatives, **18** (EIMS m/z 516 M^+; mp 236–238 °C) and **19** (EIMS m/z 606 M^+; mp 197–198 °C). As a result of this good regioselectivity, we decided to compare BTMA·ICl_2 to other iodinating reagents, ICl and *N*-iodosuccinimide. Both reagents were used with **12** under same conditions as BTMA·ICl_2, but iodination with ICl was also performed in AcOH (usual solvent for this reagent).[14] In any case, reactions resulted mainly in a mixture of 7,3′-dimethyl-6-iododiosmetin **13** and 7,3′-dimethyl-8-iododiosmetin **20**, but in various ratios. When the reactions were carried out in the system CH_2Cl_2–MeOH–$CaCO_3$, **13** was always the main product but the best regioselectivity was observed with BTMA·ICl_2 (ratios **13/20** = 10 with BTMA·ICl_2, 4.6 with ICl and 1.9 with NIS). On the other hand, ICl/AcOH provided by a slight majority (ratio **13/20** = 0.9) the compound **20**, which could be purified by TLC then crystallized (mp 267–270 °C) and identified to the 8-iodo regioisomer (a significant Overhauser effect was observed between the phenol proton and H6).

2.4. Iodination of 5-hydroxy-7-peracetylglycosyloxyflavones

Our study was then extended to the iodination of 5,7-dihydroxyflavones glycosylated at the 7 phenol group. Choice of rhoifolin (apigenin 7-neohesperidoside) **21** and diosmin (diosmetin 7-rutinoside) **22** was explained by their easy semisynthetic access from naringin and hesperidin,[15] two readily available *Citrus* flavanone glycosides. Furthermore their glycosyl chains are different, which can have an influence on the regioselectivity.



	R_1	R_2	R_3	R_4	R_5	R_6
6	H	H	H	H	OH	OMe
7	H	H	I	I	OH	OMe
8	H	H	H	H	H	OMe
9	H	H	I	I	H	OMe
10	Ac	H	H	H	OAc	OMe
11	Ac	Ac	H	H	OAc	OMe
12	Me	H	H	H	OMe	OMe
13	Me	H	I	H	OMe	OMe
14	Me	H	H	H	H	OMe
15	Me	H	I	H	H	OMe
16	Bn	H	H	H	OH	OMe
17	Bn	H	H	H	OBn	OMe
18	Bn	H	I	H	OH	OMe
19	Bn	H	I	H	OBn	OMe
20	Me	H	H	I	OMe	OMe
21	Neo [a]	H	H	H	H	OH
22	Rut [b]	H	H	H	OH	OMe
23	HNeo [c]	H	H	H	H	OAc
24	HRut [d]	H	H	H	OAc	OMe
25	mixture of 6-iodo (88%) and 8-iodo (12%) derivatives of **23**					
26	mixture of 6-iodo (90%) and 8-iodo (10%) derivatives of **24**					

[a] Neohesperidosyl; [b] Rutinosyl; [c] Hexaacetylneohesperidosyl; [d] Hexaacetylrutinosyl

Iodination was not undertaken with **21** and **22** themselves because of their insolubility in CH_2Cl_2–MeOH. Therefore they were first converted to their respective 5-hydroxy-heptaacetyl derivatives **23** and **24** by a two-steps sequence (a) Ac_2O–pyridine, rt, 48 h; (b) TFA, rt, 6 h; quantitative yield).[16] Treatment of rhoifoline derivative **23** with BTMA·ICl_2 led to the amorphous compound **25** in 96% yield. Compound **25** was homogeneous in TLC (silica gel, CH_2Cl_2–MeOH 98:2) but its ^1H NMR spectrum displayed a splitting of some characteristic signals (CH_3 of rhamnose, H2′,6′, phenol group) in a 88:12 ratio. Once more, the NMR comparative study of **23** and **25** fully agreed with a 6-iodo substitution for the major component of **25**. Finally, the observation in the ESI mass spectrum of **25** of a single peak at m/z 1021 $[M+Na]^+$ confirmed **25** to be the 6-iodo/8-iodo mixture. In the same way, 5-hydroxy-heptaacetyldiosmin **24** furnished **26**, the amorphous mixture 90/10 of the 6-iodo/8-iodo derivatives (ESIMS m/z 1051 $[M+Na]^+$).

In conclusion, BTMA·ICl_2 proved to be an excellent reagent to achieve the regioselective 6-iodination of 5,7-dioxygenated flavones and so to provide key intermediates for the synthesis of some natural biflavonoids and their analogues. The required functions are a free phenol at C5 and an alkoxy or a peracylglycosyloxy chain at C7, that is, a general pattern of substitutions available from many natural flavones. By comparison with ICl and NIS, BTMA·ICl_2 allows a better regioselectivity owing to reaction conditions (CH_2Cl_2–MeOH–$CaCO_3$ vs AcOH) but also to the reagent itself. Consequently, BTMA·ICl_2 appears to carry out regioselective 6-iodination as well as the I_2/TlOAc system without handling of a strongly toxic reagent.

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