Synthesis of 3-Iodo Derivatives of Flavones, Thioflavones and Thiochromones

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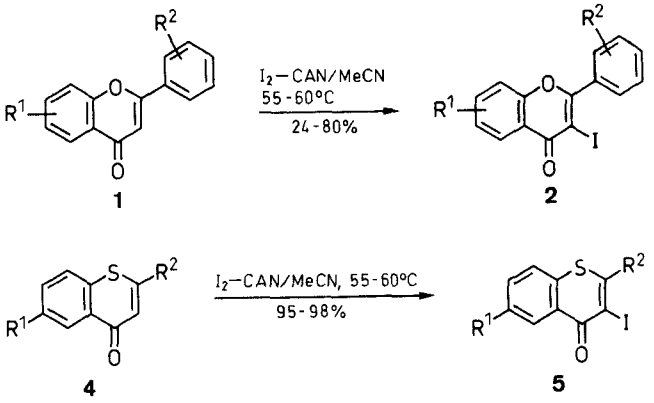
The title compounds, 2-aryl-3-iodo-4*H*-1-benzopyrans and 2-alkyl- or 2-aryl-3-iodo-4*H*-1-benzothiopyrans, were prepared by reaction of the corresponding heterocyclic derivatives with the iodine–cerium(IV) ammonium nitrate system under mild conditions. The scope and proposed mechanism of the reaction were also demonstrated.

3-Iodoflavonoids and 3-iodothioflavonoids are potential intermediates in the synthesis of C_3-linked biflavonoids. However, to our knowledge, reports of the synthesis of these compounds have been scarce. So far, only 3-iodoflavone[2] has been prepared by iodination of 3-lithioflavone. Gammile[3] has synthesized a series of 3-halochromones through enamines. But the application of this method for the preparation of 3-iodoflavones has not been demonstrated. Iqbal et al.[4] have reported a one-step synthesis of 3-iodoflavones by reaction of 2′-hydroxychalcones with the iodine/sulfuric acid/dimethyl sulfoxide system. However, according to this procedure, our repeated experiments resulted in 8-iodoflavones, instead of the desired 3-iodoflavones. Therefore, we sought to develop a new route to 3-iodoflavonoids and 3-iodothioflavonoids. The iodine–cerium(IV) ammonium nitrate (I_2–CAN) system has been used as a mild and convenient reagent system for the iodination of ketones,[5] aromatic compounds,[6] uracil derivatives,[7] and enones.[8] Flavones, thioflavones, and thiochromones also have enone structures. So, it seems promising to attempt a conversion of these compounds to their 3-iodo derivatives by the I_2–CAN system.

The flavones were treated with I_2–CAN in anhydrous acetonitrile (Scheme 1) and the results are summarized in Table 1. As shown in Table 1, the iodination of the flavones **1a–h** proceeded smoothly to give the corresponding 3-iodo derivatives **2a–h**, but the yields varied very much with the substituents. For 4′,5,7-trimethoxyflavone **1i**, 3,8-diiodo-4′,5,7-trimethoxyflavone **3** was obtained instead of the desired 3-iodo derivative. Further comparing the yields, we can find some interesting facts.

The flavones **1b,g** and **1h**, which have electron-donating group such as a methoxy or benzyloxy group at C-4′, give the 3-iodo derivatives in high yields. On the contrary, the flavones **1a** and **1c–f**, which have no electron-donating group at C-4′ afford the 3-iodo derivatives in low yields. As in the case of **1c,d,f,i**, no methoxy group at C-4′ decreases the yields. Thus, an electron-donating group at C-4′ seems to be important for high yields of 3-iodoflavones.



Scheme 1

The thioflavones **4a,b** and thiochromones **4c,d** were also treated with I_2-CAN (Scheme 1). To our surprise, all these compounds were converted nearly quantitative into their 3-iodo derivatives.

In order to rationalize the above results, we would like to propose a mechanism (Scheme 2) which involves an electrophilic attack of I^+ (produced by the interaction between I_2 and CAN) at C-3 of the substrate followed by elemination of the proton at C-3.

The attack of I^+ at C-3 gives a carbocation in which the charge is distributed only to the B-ring and the hetero

Table 1. Iodination of Flavones with I_2–CAN

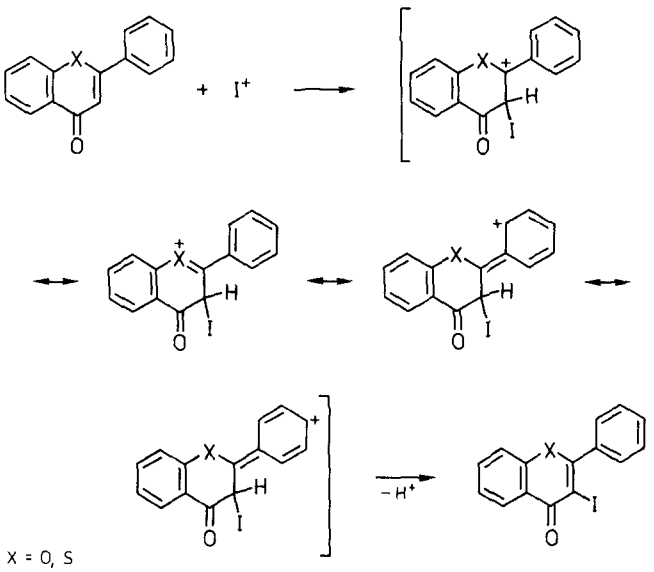
Substrate	R^1	R^2	Product	Time (h)	Yield (%)[a]	mp (°C) (CH_2Cl_2/EtOH)	Molecular Formula[b] or Lit. mp (°C)
1a	H	H	**2a**	20.0	37	127–128	128[1]
1b	H	4′-MeO	**2b**	3.0	71	149–150	$C_{16}H_{11}IO_3$ (378.2)
1c	6-MeO	H	**2c**	20.0	29	134–135	$C_{16}H_{11}IO_3$ (378.2)
1d	7-MeO	H	**2d**	20.0	27	193–194	$C_{16}H_{11}IO_3$ (378.2)
1e	H	4′-Cl	**2e**	20.0	24	158–160	$C_{15}H_8ClIO_2$ (382.6)
1f	H	2′-MeO	**2f**	20.0	30	129–131	$C_{16}H_{11}IO_3$ (378.2)
1g	7-MeO	4′-MeO	**2g**	3.5	80	187–188	$C_{17}H_{13}IO_4$ (408.2)
1h	7-MeO	4′-BnO	**2h**	3.5	73	189–190	$C_{23}H_{17}IO_4$ (484.3)
1i	5,7-$(MeO)_2$	4′-MeO	–[c]	2.0	–	–	–

[a] Yields represent isolated, purified products.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.30, I ±0.39.
[c] 3,8-Diiodo derivative **3** was obtained in 41% yield.

atom. This is consistent with the fact that the group on the A-ring does not have distinct effect on the iodination at C-3.

In the case of thioflavones and thiochromones, the sulfur lone pair is much basic and strongly stabilizes the intermediate cation. Therefore, the iodination reactions are not sensitive to the substituent effects and the 3-iodo derivatives are obtained in good yields.

Whereas with flavones, the oxygen lone pair is less basic and the involvement of the B-ring now dominates. So, the great importance of the group at C-4′ is well demonstrated. The electron-donating group at C-4′ stabilizes the intermediate cation and increases the rate of the iodination at C-3. Therefore the corresponding 3-iodo derivative is obtained in good yield. It follows that the 2′-methoxy group should also be able to stabilize the intermediate cation. But in fact 3-iodo-2′-methoxyflavone is obtained in low yield. This is possibly due to the steric hindrance to the attack of a bulky I^+ at C-3 caused by the 2′-methoxy group.



Scheme 2

Table 2. Iodination of Thioflavone and Thiochromones

Substrate	R^1	R^2	Product	Time (h)	Yield (%)[a]	mp (°C) (solvent)	Molecular Formula[b]
4a	H	Me	**5a**	18.0	95	152–153 (CH_2Cl_2/hexane)	$C_{10}H_7IOS$ (302.1)
4b	Me	Me	**5b**	20.0	97	150–151 (MeOH)	$C_{11}H_9IOS$ (316.1)
4c	H	Ph	**5c**	20.0	98	139–140 (CH_2Cl_2/MeOH)	$C_{15}H_9IOS$ (364.2)
4d	Me	Ph	**5d**	18.0	98	126–128 (CH_2Cl_2/MeOH)	$C_{16}H_{11}IOS$ (378.2)

[a] Yields represent isolated, purified products.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.19, I ±0.37.

Table 3. Spectroscopic Data of Compounds **2**, **3** and **5**

Product	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	MS (70 eV) m/z (%)
2a	1654, 1551, 1463, 1057, 755, 691	7.30–7.90 (8H, m, ArH), 8.29 (1H, dd, J = 2.0, 8.0, 5-H)	348 (M^+, 100), 221 (48), 165 (42)
2b	1652, 1611, 1505, 1250, 824, 760	3.90 (3H, s, OMe), 7.01 (2H, d, J = 8.8, 3′-H, 5′-H), 7.30–7.92 (5H, m, ArH), 8.26 (1H, d, J = 8.0, 5-H)	378 (M^+, 100), 258 (98), 251 (70)
2c	1642, 1610, 1488, 1325, 1015, 769	3.91 (3H, s, OMe), 7.15–7.95 (8H, m, ArH)	378 (M^+, 100), 251 (40)
2d	1645, 1621, 1332, 1056, 768, 695	3.90 (3H, s, OMe), 6.80–7.15 (2H, m, ArH), 7.40–7.90 (5H, m, ArH), 8.19 (1H, d, J = 8.8, 5-H)	378 (M^+, 100), 251 (30)
2e	1646, 1613, 1464, 1329, 756	7.31–7.95 (7H, m, ArH), 8.27 (1H, dd, J = 2.0, 8.0, 5-H)	382 (M^+, 100), 255 (25)
2f	1649, 1614, 1465, 1325, 1017, 754	3.85 (3H, s, OMe), 6.95–7.95 (7H, m, ArH), 8.29 (1H, d, J = 8.5, 5-H)	378 (M^+, 100), 251 (10)
2g	1642, 1612, 1502, 1253, 1171, 833	3.89 (6H, s, OMe × 2), 6.80–7.10 (4H, m, ArH), 7.77 (2H, d, J = 8.9, 2′-H, 6′-H), 8.16 (1H, d, J = 8.7, 5-H)	408 (M^+, 100), 281 (26), 258 (40)
2h	1609, 1501, 1241, 1009, 836, 759	3.38 (3H, s, OMe), 5.14 (2H, s, $PhCH_2$), 6.70–7.15 (4H, m, ArH), 7.50 (5H, m, C_6H_5), 7.77 (2H, d, J = 8.9, 2′-H, 6′-H), 8.16 (1H, d, J = 8.8, 5-H)	484 (M^+, 52), 357 (8), 91 (100)
3	1649, 1603, 1584, 1288, 1030, 832	3.91 (3H, s, OMe), 4.03 (6H, s, OMe × 2), 6.46 (1H, s, 6-H), 7.04 (2H, d, J = 9.0, 3′-H, 5′-H), 8.04 (2H, d, J = 9.0, 2′-H, 5′-H)	564 (M^+, 100), 518 (15), 437 (10)
5a	1615, 1579, 1295, 794, 751, 684	2.63 (3H, s, Me), 7.40–7.70 (3H, m, ArH), 8.50 (1H, dd, J = 2.0, 8.0, 5-H)	302 (M^+, 100), 175 (10), 147 (50)
5b	1617, 1599, 1094, 802, 765, 738	2.49 (3H, s, 6-Me), 2.63 (3H, s, 2-Me), 7.35–7.50 (2H, m, 7-H, 8-H), 8.35 (1H, s, 5-H)	316 (M^+, 100), 189 (10), 161 (40)
5c	1623, 1532, 1436, 1285, 1099, 736	7.30–7.70 (8H, m, ArH), 8.35–8.75 (1H, m, 5-H)	364 (M^+, 100), 237 (82), 165 (75)
5d	1619, 1594, 1439, 1105, 740, 693	2.51 (3H, s, Me), 7.30–7.65 (1H, m, ArH), 8.42 (1H, s, 5-H)	378 (M^+, 100), 251 (70), 208 (42)

The attack of I^+ at aromatic ring and at C-3 are competitive. So, if the electron-donating groups are not at C-4′, the aromatic ring will be more activated than C-3, thus, the iodination will occur at the aromatic ring. This causes the reaction to be complicated and to give low yields of 3-iodo derivatives. It is especially true in the case of compounds **1c,d,f,i**.

Therefore, from the experimental results and the mechanistic discussion, some generalizations about the reaction can be made as follows: i. In the case of flavones, an electron-donating group at C-4′ is important for the high yields of the 3-iodoflavones. ii. As for thioflavones and thiochromones, the yields of their 3-iodo derivatives are generally high, regardless of the substituents. iii. The aromatic rings should not be very activated. Otherwise, the reaction will give a complex mixture, and the desired 3-iodo derivatives will not be obtained. iv. Furthermore, it seems to be reasonable to predict that chromones will give low to moderate yields of the corresponding 3-iodochromones. On the contrary, high yields of 1-alkyl-3-iodo-4-(1*H*)-quinolinones are anticipated.

In summary, we have developed a mild and convenient procedure for the preparation of 3-iodo derivatives of flavones, thioflavones and thiochromones and proposed a reasonable mechanism which accommodated our experimental data well.

The flavone **1a** was commercially available. The flavones **1b–i** were prepared by condensation of a 2-hydroxyacetophenone and a benzaldehyde in alkaline solution followed by oxidative cyclization.[9] The thioflavones **4a,b** and the thiochromones **4c,d** were prepared by condensation of a β-oxo ester (ethyl benzoylacetate or ethyl acetoacetate) and a thiophenol in polyphosphoric acid according to a procedure of Razdan.[10]

Melting points were measured with a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on Nicolet 170SX FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC-80 or FT-80 spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were obtained on a ZAB-HS instrument. Microanalysis were performed at the Instrumental Analysis and Research Centre, Lanzhou University.

2-Aryl-3-iodo-4*H*-1-benzopyrans 2 and 2-Alkyl or 2-Aryl-3-iodo-4*H*-1-benzothiopyrans 5; General Procedure:

A mixture of a substrate (1.0 mmol), I_2 (1.2 mmol) and CAN (1.1 mmol) in anhydr. MeCN (4 mL) was stirred at 55–60 °C under Ar. The reaction was continued until the substrate disppeared (determined by TLC analysis). Then the mixture was poured into a cold aq $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc (9:1 to 4:1) as eluants **(2a–h)** or by recrystallization **(5a–d)**.

Iodination of 5,7-Methoxy-2-(4-methoxyphenyl)-4*H*-1-benzopyran (1i):

The reaction was carried out in 1 mmol scale as described above. After usual workup, the residue was purified by column chromatography on silica gel using benzene/EtOAc (4:1) as eluant to give 3,8-diiodo-5,7-trimethoxy-2-(4-methoxyphenyl)-4*H*-1-benzopyran **(3)**; yield: 230 mg (41 %); mp 227–228 °C (recrystallized from CH_2Cl_2/EtOH).

$C_{18}H_{14}I_2O_5$	calc.	C 38.33	H 2.50	I 44.99
(564.1)	found	38.41	2.63	44.50

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