Hypervalent Iodine Oxidation of Flavanones: A New Synthesis of Methyl 2-Aryl-2,3-dihydrobenzofuran-3-carboxylates by 1,2-Aryl Shift

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Flavanones (**1**), on oxidation with (diacetoxyiodo)benzene–sulfuric acid (DIB–H_2SO_4) or (hydroxy)-tosyloxy)iodo)benzene (HTIB) in trimethyl orthoformate, undergo facile ring contraction by 1,2-aryl shift, thereby yielding methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates (**4**) as major products (40—80%). *cis*-3-Methoxyflavanones (**5**) and flavones (**3**) are the minor products formed in variable ratios.

The use of hypervalent iodine reagents to bring about various interesting transformations in flavonoids has been the subject of our recent papers.[1—7] In our earlier reports, we have shown that hypervalent iodine oxidation of flavanones (**1**) using (hydroxy(tosyloxy)iodo)-benzene (HTIB)[8] in acetonitrile[5] and methanol[6] offers interesting routes for the formation of isoflavones (**2**) and flavones (**3**) respectively.

Although oxidation of **1** with HTIB in methanol mainly gave flavones, in a few cases side products such as methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates (**4**) and *cis*-3-methoxyflavanones (**5**) were also isolated in minor amounts.[9] This observation coupled with the fact that oxidation of aryl ethyl ketones[10] with hypervalent iodine reagents in trimethyl orthoformate (TMOF) leads to 1,2-aryl shift with the formation of 2-arylpropanoates, prompted us to investigate the oxidation of flavanones (**1**) with (diacetoxyiodo)benzene–sulfuric acid (DIB–H_2SO_4) and HTIB in TMOF. The results of this study are reported herein.

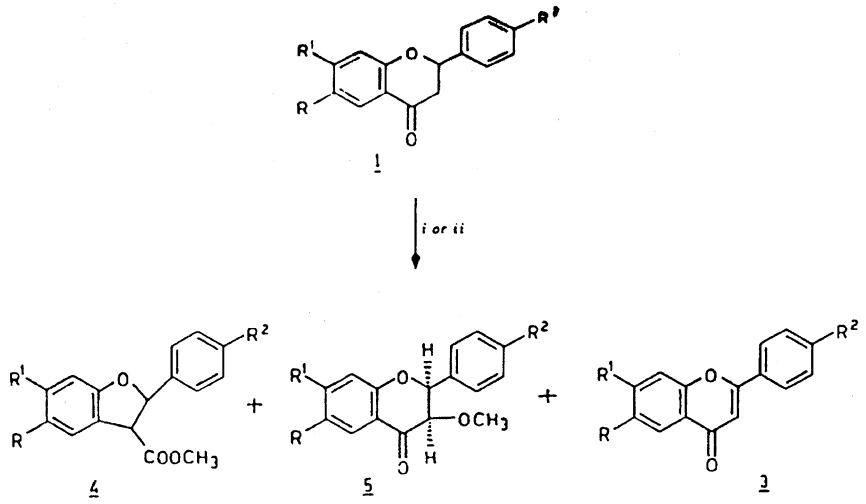
Flavanones (**1a—g**), upon hypervalent iodine oxidation with DIB–H_2SO_4 or HTIB in TMOF at room temperature, yielded methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates (**4a—g**) as major products (40—80%, Scheme 1). *cis*-3-Methoxyflavanones (**5a—d, 5g**) and flavones (**3a—d, 3g**) isolated from the oxidation of (**1a—d, 1g**), were found to be the minor products and formed in varying ratios. The oxidation of **1e** and **1f** (R=CH_3) did not give **5** even in trace amounts. A notable exception of this oxidative approach where no formation of **4** or **5** occurred, was the case of flavanone **1h**, which contains *p*-methoxy substituent in the 2-aryl ring. Thus, the reaction of **1h** with DIB–H_2SO_4 or HTIB resulted in the formation of a mixture of isoflavone (**2h**, 80%) along with flavone (**3h**, 20%). All the products were separated by column chromatography and characterized by spectral data (IR, ^{1}H NMR and mass spectra). Although the products **4** are stereochemically single isomers showing approximately 10 Hz of coupling constants between $C_{(2)}$–H and $C_{(3)}$–H in ^{1}H NMR, their exact configuration are not yet certain.

A plausible mechanism for the above transformations is depicted in Scheme 2. As suggested by us in the oxidation of alkyl aryl ketones,[10] a key step of the reaction is the formation of hypervalent iodine intermediate **8** by the electrophilic attack of I(III) reagent at $C_{(3)}$ of enol ether **7** (generated in situ **1**→**6**→**7**) anti to $C_{(2)}$–aryl group. Subsequently, **8** can lead to the products **4**, **5**, and **2** via paths a, b, and c, respectively. Path a involves (i) 1,2-aryl (benzene ring) migration to give **9**, (ii) addition of methanol to **9** affording ortho ester **10**, and (iii) hydrolysis of **10** to produce **4**. Path b consists of nucleophilic displacement of iodobenzene by methoxy group to afford **5**. Since this process is accompanied by inversion, the resulting products **5** have cis-relationship[11] between $C_{(3)}$–H and $C_{(2)}$–H (confirmed by ^{1}H NMR, $J_{2,3}=J_{3,2}$=approx. 2 Hz).

It seems likely that **5** will undergo loss of a molecule of methanol to give **3** by trans elimination. The process of elimination involving $C_{(2)}$–H and $C_{(3)}$–OMe having trans stereochemistry was supported by the isolation and identification of **3** from a separate experiment in which a solution of **5** was stirred for 2 h. This observation also provides a possible reason for relatively less developments in the area of *cis*-3-oxygenated flavanones.

Path c, which explains the formation of isoflavone (**2h**), is similar to our previous study[5] on the synthesis of **2**. In the present case, the migratory aptitude of $C_{(2)}$-*p*-methoxyphenyl moiety, is a predominating factor and thus results in the migration of pyran ring instead of benzene ring.

Finally, it is to be emphasized that hypervalent iodine oxidation of flavanones discussed in the present study constitutes a new and convenient method for the



Compd. No. 1—5	R	R^1	R^2
a	H	H	H
b	H	H	Cl
c	Cl	H	H
d	Cl	H	Cl
e	CH_3	H	H
f	CH_3	H	Cl
g	Cl	CH_3	H
h	Cl	H	OCH_3

(i) IBD–H_2SO_4/TMOF.
(ii) HTIB/TMOF.
Scheme 1.

synthesis of methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates (**4**). This method also provides a one step synthesis of *cis*-3-methoxyflavanones (**5**) from readily accessible flavanones, which are, otherwise, very difficult to obtain and less established. Furthermore, this method is superior to the literature procedure for the synthesis of **4** involving toxic thallium salts.[12]

Experimental

IR spectra were recorded on a Perkin–Elmer 842 IR spectrophotometer in Nujol mulls. ^{1}H NMR spectra were scanned on Perkin–Elmer R-32 or JEOL FX-90 MHZ machine using $CDCl_3$ as solvent and Me_4Si as an internal standard. TLC was carried out on silica gel coated plates using iodine as developing agent and the compounds were separated over a column of silica gel (100—200 mesh) using ethyl acetate–hexane (1 : 9) as eluent.

Oxidation of Flavanones with (Diacetoxyiodo)-benzenesulfuric Acid or (Hydroxy(tosyloxy)iodo)-benzene. General Procedure: To a solution of flavanone (**1** 0.001 mol) in trimethyl orthoformate (25 ml) was added 2—3 drops of concd sulfuric acid with stirring. To the resulting reaction mixture was added (diacetoxyiodo)-benzene (0.0011 mol) and the solution was stirred at room temperature for overnight. The progress of the reaction was monitored by TLC. The solvent (TMOF) was removed in vacuo and then water was added. The solution was stirred for 2—3 h and the resulting mixture was extracted with dichloromethane (3×50 ml). The combined organic phase was washed with $NaHCO_3$ solution followed by water and dried (Na_2SO_4). Removal of the solvents at reduced pressure yielded crude products as oil. Pure products were obtained by passing crude mixture through a column of silica gel using ethyl acetate–hexane (1 : 9) as eluent (Table 1).

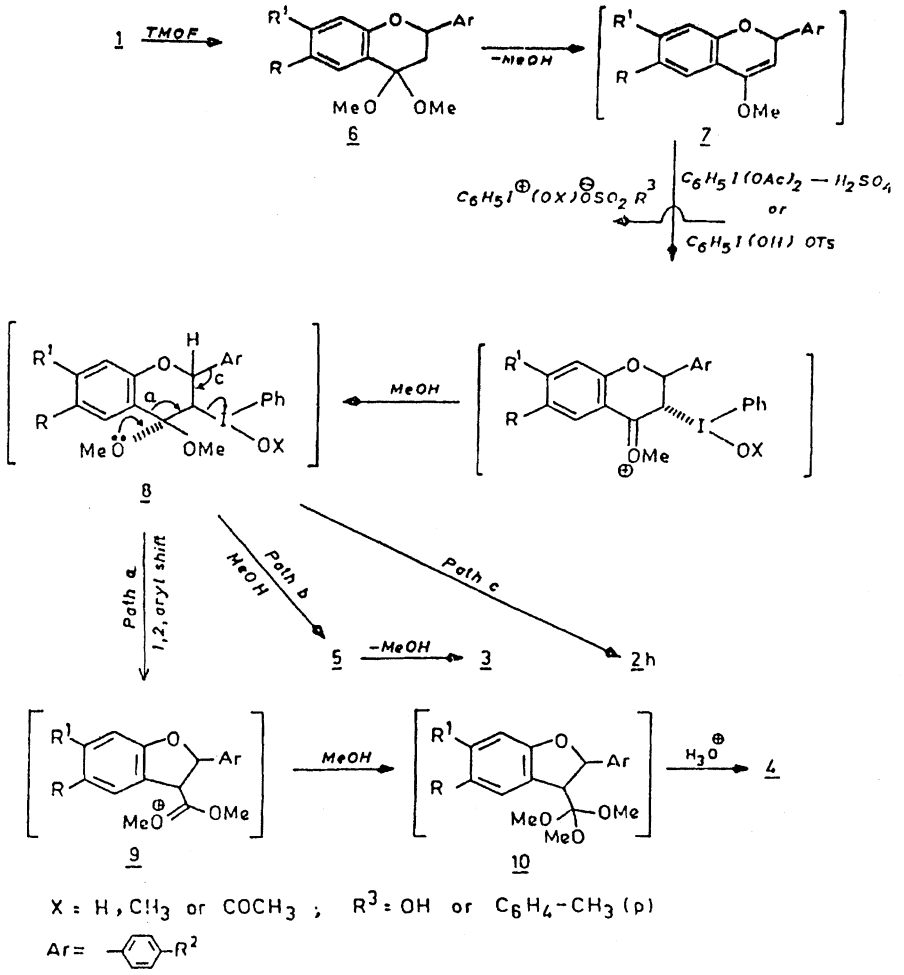
Similar experiment as described above was repeated using HTIB in place of DIB–H_2SO_4, which after usual work up yielded crude products as oil. The products were purified using column chromatography as described above (Table 1 summarizes the % yields of the products). The spectral data of the products are given below:

4b: IR (Nujol) ν=1740 cm^{-1} (C=O, s). ^{1}H NMR

Table 1. Yields of Compounds **4**, **5**, and **3**

Compd.	Yield[a]	Compd.	Yield[a]	Compd.	Yield[a]
4	%	**5**	%	**3**	%
a	50 (40)[b]	**a**	35 (27)[b]	**a**	15 (12)[b]
b	70 (60)	**b**[c]	10 (—)	**b**	20 (18)
c	50 (43)	**c**	40 (36)	**c**	10 (8)
d	40 (35)	**d**	40 (34)	**d**	20 (16)
e	80 (75)	**e**	—	**e**	20 (16)
f	80 (75)	**f**	—	**f**	20 (16)
g	55 (47)	**g**[c]	5 (—)	**g**	40 (35)
h	—	**h**	—	**h**	20 (18)

a) Yields are based on the ^{1}H NMR of crude mixture. b) Yields in parentheses are based upon the isolated pure products. c) Only seen in ^{1}H NMR of crude mixture. d) The spectral data for compounds **4a**, **4e**, and **4g** were found to be in close proximity to that reported in the literature.[12] New compounds were confirmed by spectral data (IR, ^{1}H NMR, and mass/. or satisfactory elemental (C, H) analysis.



Scheme 2.

($CDCl_3$) δ=3.70 (s, 3H, C_3–$COOCH_3$), 4.10 (d, 1H, C_3–H), 6.10 (d, 1H, C_2–H), 6.60—7.85 (m, $8H_{arom.}$).

4c: IR (Nujol) ν=1735 cm^{-1} (C=O, s). ^1H NMR ($CDCl_3$) δ=3.70 (s, 1H, C_3–$COOCH_3$), 4.10 (d, 1H, C_3–H), 6.10 (d, 1H, C_2–H), 6.60—7.85 (m, $9H_{arom.}$).

4d: IR (Nujol) ν=1740 cm^{-1} (C=O, s). ^1H NMR ($CDCl_3$) δ=3.70 (s, 3H, C_3–$COOCH_3$), 4.15 (d, 1H, C_3–H), 6.05 (d, 1H, C_2–H), 6.70—8.10 (m, $7H_{arom.}$).

4f: IR (Nujol) ν=1740 cm^{-1} (C=O, s). ^1H NMR ($CDCl_3$) δ = 2.25 (s, 3H, C_5–CH_3), 3.75 (s, 3H, C_3–$COOCH_3$), 4.15 (d, 1H, C_3–H), 6.00 (d, 1H, C_2–H), 6.70—7.80 (m, $8H_{arom.}$).

MS (70 eV) *m/z* 304 (M^+, 22), 302 (M^+, 58), 272 (41), 271 (30), 270 (100), 269 (26), 245 (15), 244 (25), 243 (45), 242 (50); $J_{2,3}$=$J_{3,2}$=approx. 10 Hz for compounds **4b**—**f**.

5a: IR (Nujol) ν=1675 cm^{-1} (C=O, s). ^1H NMR ($CDCl_3$) δ=3.15 (s, 1H, C_3–OCH_3), 3.65 (d, 1H, C_3–H), 5.20 (d, 1H, C_2–H), 6.90—7.80 (m, $9H_{arom.}$).

5c: IR (Nujol) ν=1680 cm^{-1} (C=O, s). ^1H NMR ($CDCl_3$) δ=3.20 (s, 3H, C_3–OCH_3), 3.70 (d, 1H, C_3–H), 5.25 (d, 1H, C_2–H), 6.95—7.90 (m, $8H_{arom.}$).

MS (70 eV) *m/z* 290 (M^+, 21), 288 (M^+, 57), 258 (38), 256 (100), 228 (55).

5d: IR (Nujol) ν=1670 cm^{-1} (C=O, s). ^1H NMR ($CDCl_3$) δ=3.30 (s, 3H, C_3–OCH_3), 3.75 (d, 1H, C_3–H), 5.35 (d, 1H, C_3–H), 7.00—7.80 (m, $8H_{arom.}$). $J_{2,3}$=$J_{2,3}$=approx. 2 Hz for compounds **5a**—**d**.[11]

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