HYPERVALENT IODINE OXIDATION OF FLAVONOLS USING [HYDROXY(TOSYLOXY)IODO]-BENZENE IN METHANOL

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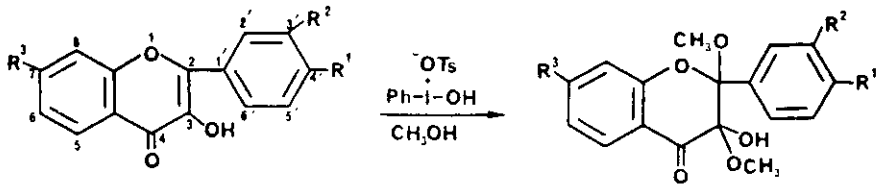
Abstract - Hypervalent iodine oxidation of various flavonols (1a-1f) and α-naphthoflavonol (3) using [hydroxy(tosyloxy)iodo]benzene (HTIB) in methanol leads to the formation of 2,3-dimethoxy-3-hydroxyflavanones (2a-2f) and 2,3-dimethoxy-3-hydroxy-α-naphthoflavanone (4) respectively. HTIB resembles periodic acid in its oxidative behavior towards flavonols.

A number of papers dealing with photooxygenation[1], superoxide anion[2] and base catalysed oxygenation reactions[3] of flavonols (1) have appeared. The object of these oxygenation reactions was to demonstrate a non-enzymatic model reaction for the biological oxygenation[4] of 1, while other oxidation reactions were carried out with a view towards establishing the behavior of various oxidizing agents upon the flavonol nucleus (1)[5].

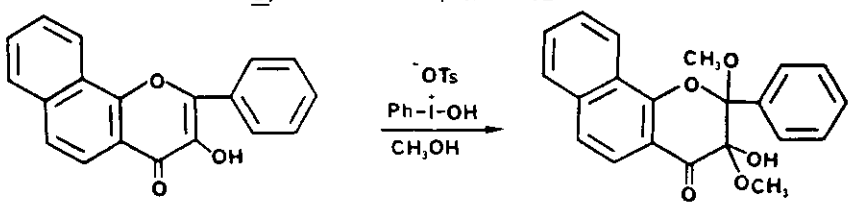
These observations, coupled with the fact that oxidation of various chalcones, olefins and acetophenones with [hydroxy(tosyloxy)iodo]benzene (HTIB) in methanol leads to rearranged products[6], prompted us to investigate the oxidation behavior of 1 with HTIB in methanol.[7]

We now find that the reaction of 1 with a slight excess of HTIB in methanol occurs spontaneously and the corresponding 2,3-dimethoxy-3-hydroxyflavanones [methyl 3-hemiacetals of 2-methoxy 3,4-flavandione (2)] are formed in high yield. α-Naphthoflavonol (3) also undergoes same type of oxidation and 4 is formed in good yield.



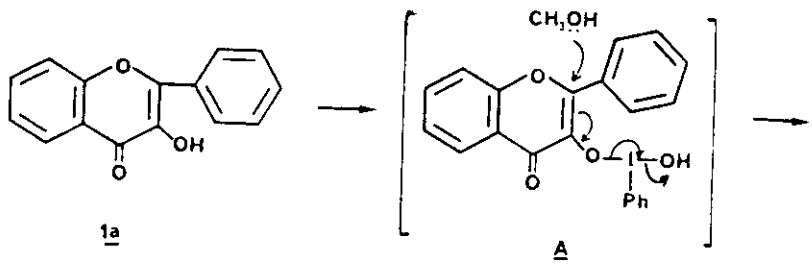
1 2

1a, $R^1 = R^2 = R^3 = H$
1b, $R^1 = R^2 = H$; $R^3 = OMe$
1c, $R^1 = OMe$; $R^2 = R^3 = H$
1d, $R^1 = R^3 = OMe$; $R^2 = H$
1e, $R^1 = R^2 = OMe$; $R^3 = H$
1f, $R^2 = R^3 = H$; $R^1 = Cl$



3 4

Formation of hemiacetals of type 2 has been previously reported from the oxidation of 1 with periodic acid in methanol by Smith et al.[5b] These workers showed that flavonol behaves like o-methoxyphenol (5) in periodic acid oxidation. We also interpret our results on the basis of the mechanism proposed by Smith et al., for the periodic acid oxidation. The first step is the formation via ligand transfer of intermediate [A]. In a subsequent step nucleophilic attack of methanol occurs at C(2) along with reduction cleavage of the -O-I(III) bond and acetal 6 is formed. Acetal 6 readily forms hemiacetal 2 with methanol under the reaction conditions. The stereochemistry of the hemiacetals (2a-f, 4) has not been assigned.



1a A

6 2a

Becker[5a] also obtained hemiacetal 2a from oxidation of 1a with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methanol and explained the formation of 2a by a radical mechanism.

Thus, the present study reveals that flavonols under hypervalent iodine oxidation using HTIB in MeOH behave like a phenol rather than an α,β-unsaturataed ketone or 1,2 diketone which could lead to rearranged products.[6] In this sense HTIB resembles periodic acid in its oxidation characteristics. This is an important addition to our growing knowledge of the oxidative capacity of organic hypervalent iodine reagents. Periodic acid is a relatively mild and selective oxidizing agent.[8] It is interesting to note that in the present case, HTIB does not attack the relatively activated aromatic rings.

The properties (mp and ir spectral data) of the products (2a-d) are available in literature and are in agreement with our data. However, mps of the products are variable and depend on the rate of heating. ^{1}HNMRs of all the compounds were determined and found to be in agreement with the assigned structure. The nmr spectra of all the hemiacetals showed two characteristic singlets due to two methoxy group protons (~δ3.0) Data on 2 and 4 are given in Table 1. New compounds 2e-2f, and 4 were confirmed by correct elemental analyses.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}HNMR spectra were recorded at 60MHz as $CDCl_3$ solutions with TMS as internal reference. Chemical shifts are given in ppm(δ). Hydroxyl signals were identified by deuteration.

[(Hydroxytosyloxy)iodobenzene (HTIB).

HTIB is prepared by the reaction of iodobenzene diacetate and p-toluenesulfonic acid according to conditions of Neiland, Karele[9a] and Koser and Wettach.[9b]

Flavonols (1a-1f).

Flavonol (1a) is commercially available (Aldrich) and other flavonols (1b-1f) are synthesized according to the Alger-Flynn-Oyamada reaction[10] with minor modifications involving H_2O_2 oxidation of various o-hydroxychalcones. Thus, 1b had mp 181-182°C (lit.[10a] mp 181°C); 1c had mp 234-235°C (lit.[10a] mp 235°C); 1d had mp 195-195.5°C (lit.[10a] 195°C); 1e had mp 202.5-203°C (lit.[10a] mp 203°C); 1f had mp 199-200°C (lit.[11] mp 198°C).

α-Naphthoflavonol (3).

Compound (3) is available from our recent study on the hypervalent iodine oxidation of α-naphthoflavone with iodobenzene diacetate in methanolic potassium hydroxide and subsequent acidic hydrolysis of crude dimethylacetal thus obtained gives pure crystalline product 3, mp 214-215°C.[12]

Oxidation of Flavonols with [Hydroxy(tosyloxy)iodo]benzene (HTIB) in Methanol. General Procedure

To a solution or suspension of flavonol (1, 3) (2.0 mmol) in methanol (20ml) was added solid [hydroxy(tosyloxy)iodo]benzene (2.2 mmol) rapidly and the mixture was shaken. All the reactants dissolved and a colorless crystalline product separated out after about 5 min. Filtration followed by washing with cold methanol (5-10ml) gave almost pure product (2, 4). Recrystallization was carried out from methanol. Compounds 2b and 2d did not separate out of the solution from the reaction mixture. Concentration of the reaction mixture solution in vacuo followed by addition of methanol yielded crystalline products.

Table 1

Compd.	mp °C[a](Lit.mp)	Yield%[b]	^{1}HNMR data δ			
			C_2-OCH_3, C_3-OCH_3,	OCH_3 aromatic ring	-OH	Aromatic Protons
2a	144-146 (146[5a]; 151-152[5b])	65	2.98,3.07		4.73	6.98-8.05
2b	139-142 (142-144.5[5b])	72	3.00,3.09	3.90	4.45	6.62-8.00
2c	162-163 (162-164[5b])	75	3.02,3.08	3.85	4.12	6.90-8.18
2d	167-169 (169-172[5b])	68	3.02,3.11	3.89, 3.92	4.30	6.60-8.02
2e	168-71[c]	77	3.03,3.09	3.95	4.38	7.02-8.10
2f	156-159[c]	73	3.00,3.07		4.00	7.04-8.05
4	140-141[c]	71	3.00,3.05		4.85	7.31-8.62

a. All compounds lost methanol upon heating, turned yellow at characteristic temperatures and finally melting over a range.

b. Based on isolated crystalline products with respect to amount of flavonol used. The actual yields of the products (from nmr and tlc) were more than 95%.

c. Analyses. 2e, Calcd for $C_{19}H_{20}O_7$: C, 63.32; H, 5.59. Found C, 63.05; H, 5.68. 2f, Calcd for $C_{17}H_{15}ClO_5$: C, 60.98; H, 4.48; Cl, 10.61. Found C, 60.75; H, 4.40; Cl, 10.39. 4, Calcd for $C_{21}H_{18}O_5$: C, 72.00; H, 5.14. Found, C, 72.35, H, 5.04.

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