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Hypervalent Iodine Oxidation of *o*-Aminochalcones: A Novel Synthesis of 3-(β-Styryl)-2,1-benzisoxazoles

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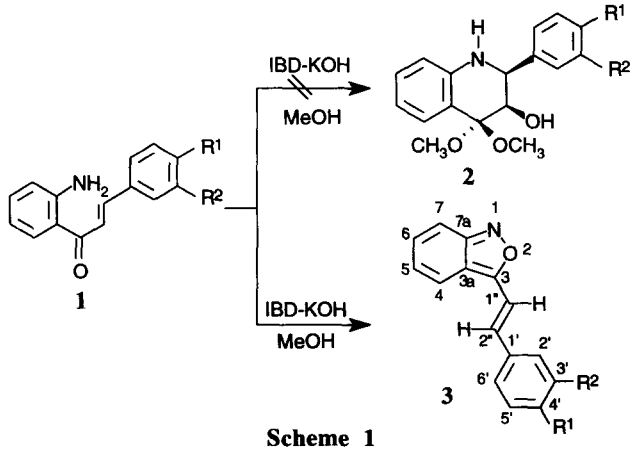
Abstract: Hypervalent iodine oxidation of *o*-aminochalcones using $C_6H_5I(OAc)_2$-KOH/MeOH leads to a novel and useful route for the synthesis of 3-(β-styryl)-2,1-benzisoxazoles. A plausible mechanism for this novel rearrangement is proposed. © 1997 Elsevier Science Ltd.

Oxidation of enolizable ketones with iodobenzene diacetate (IBD) in methanolic potassium hydroxide is known to result in the efficient formation of α-hydroxydimethylacetals.[1,2] When applied to α,β-unsaturated ketones lacking an enolizable proton, the corresponding β-methoxy-α-hydroxydimethylacetals are formed instead.[3] *o*-Hydroxychalcones (a typical class of α,β-unsaturated ketones) under similar conditions afford *cis*-3-hydroxyflavanone dimethylacetals which upon acid hydrolysis (aq. AcOH) provides a novel and convenient route to the relatively rare and not readily accessible *cis* -3-hydroxyflavanones.[4-6]

These observations coupled with known stability of the amino functionality under these conditions,[7,8] prompted us to investigate the oxidation of *o* -aminochalcones (**1**) using IBD-KOH/MeOH. The objective is to synthesize *'N'* analogs of *cis* -3-hydroxyflavanones under the assumption that NH_2 would behave similar to OH as an intramolecular participant to yield a quinolone derivative **2** (Scheme 1).



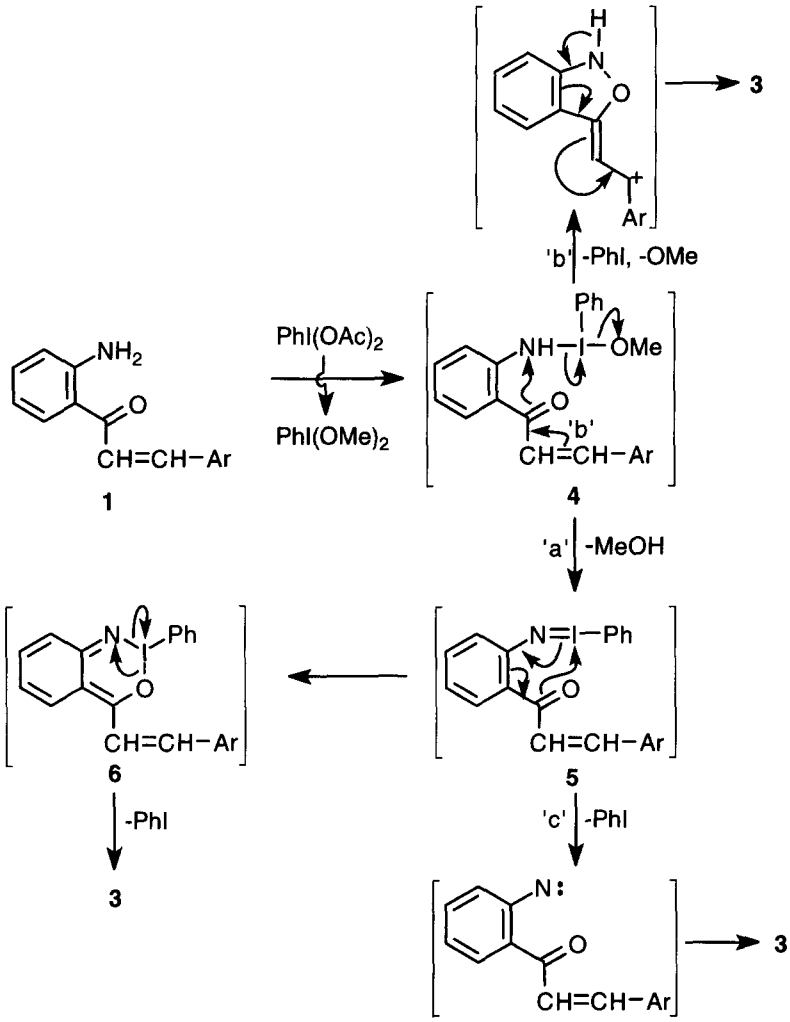
1,3	R^1	R^2	Yield (%)
a	H	H	88
b	OMe	H	82
c	Cl	H	84
d	Me	H	83
e	Br	H	82
f	OMe	OMe	83

Scheme 1

The treatment of *o*-aminochalcone, **1a**, with IBD (1·1 equivalents) in excess of methanolic KOH,[4,5] however, afforded upon purification a yellow crystalline product (mp 124-25 °C) that is not the expected *'N'* analog of *cis*-3-hydroxyflavanone dimethylacetal (**2**). Analysis of the spectral properties of the product (IR,

^{1}H NMR, ^{13}C NMR, and HRMS) ruled out the possible formation of 2-phenyl-4(1H)-quinolone or the isomeric dehydrogenated products such as 3-phenyl-4(1H)-quinolone, 2-phenylideneindoxyl, etc. as indicated by the comparison to the reported mp(s) and spectral properties of these compounds. The structural features of the yellow product imply the novel formation of a 3-(β-styryl)-2,1-benzisoxazole, (**3a**). A detailed study revealed that this transformation is general in nature as various substituted *o*-aminochalcones, **1b-f**, upon reaction with IBD-KOH/MeOH afforded the corresponding 3-(β-styryl)-2,1-benzisoxazoles, **3b-f**, in good yields (Scheme 1) thus providing a novel route for the general synthesis of these 3-substituted anthranils.

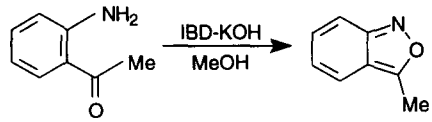
A plausible mechanism for the novel conversion **1** ⟶ **3** is outlined in Scheme 2. This transformation probably involves the attack of the I(III) reagent $PhI(OMe)_2$ (generated from IBD-KOH/MeOH) on the amino group to give intermediate **4** which could lose a proton under the basic conditions forming an iodonium ylide type intermediate **5** (route 'a'). The latter may undergo intramolecular cyclization to give **6**. Finally, the cycloadduct **6** can lose a molecule of iodobenzene to afford 3-(β-styryl)-2,1-benzisoxazole (**3**). Other possibilities such as routes 'b' and 'c' cannot be ruled out.



Scheme 2

The physical and spectral data of various 2,1-benzisoxazoles, **3**, obtained earlier[9] by the thermal decomposition of *o*-azidochalcones has not been documented. Consequently, 2,1-benzisoxazole derivatives **3** are now fully characterized by elemental analyses and spectral methods.[10] The IR spectra of **3** clearly show the absence of the carbonyl and amino groups. The ^{1}H NMR spectra indicate the *trans* relationship of 1"-H and 2"-H (J = ~16.37 Hz). The HRMS show the molecular ion peak as the base peak and the fragmentation pattern suggests that some isomerization has taken place in 2,1-benzisoxazoles prior to cleavage.

2,1-benzisoxazoles, **3**, are important precursors for the synthesis of 3-aryl-4-quinolones and 2-arylideneindoxyls.[9] In view of the potential application as thermostable explosives,[11] and interesting biological activity (antiinflammatory,[12] antituberculotic,[13] etc.) associated with 2,1-benzisoxazoles ring system, this novel procedure may be of preparatively value. Under similar reaction conditions, *o*-aminoacetophenone is cyclized to 3-methyl-2,1-benzisoxazole in 50% yield.



In conclusion, the present study provides a useful and novel route to the synthesis of 3-(β-styryl)-2,1-benzisoxazoles. This manipulatively easy process avoids the use of azido derivatives which are hazardous and otherwise not as readily accessible when compared to amino compounds.

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10. **General Procedure–Prepartion of the 3-(β-Styryl)-2,1-benzisoxazoles, 3a-f:** *o*-Aminochalcone[14,15] (**8**, 4 mmol) was added to a stirred solution of potassium hydroxide (12 mmol) in methanol (40 mL) followed by the gradual addition of iodobenzene diacetate (1.42 g, 4.4 mmol). The reaction mixture was stirred overnight until the starting material disappeared as followed by TLC. The solvent was removed under reduced pressure and the residue was stirred in water (20 mL) for 15-20 min. The pale orange precipitate formed was filtered, washed with water, dried and crystallized from methanol or alternatively purified by column chromatography using silica gel (eluent, ethylacetate-hexane: 1:20) to afford 3-(β-styryl)-2,1-benzisoxazole (**3**).

3a: yield: 88%; mp 124-25°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.98 (dd, 1H, 5-H, J = 6.5 Hz), 7.22-7.31 (m, 2H, 6-, 1"-H), 7.33-7.44 (m, 3H, 3'-, 4'-, 5'-H), 7.50-7.65 (m, 5H, 4-, 7-, 2"-, 2'-, 6'-H); IR (Nujol)

1640, 1630, 1518 cm^{-1} (C=N and C=C); ^{13}C NMR (75.5 MHz); δ = 163.458 (C-3), 115.679 (C-3a), 115.173 (C-4), 119.819 (C-5), 123.998 (C-6), 111.940 (C-7), 157.352 (C-7a), 135.579 (C-1'), 127.211 (C-2', C-6'), 128.903 (C-3', C-5'), 129.332 (C-4'), 130.851 (C-1"), 135.579 (C-2"); HRMS (m/z); 222.0917 (M^++1, 22.2), 221.0867 (M^+, 100), 193 (47), 178 (40); Anal Calcd. for $C_{15}H_{11}NO$: C, 81.45; H, 4.97; N, 6.33. Found: C, 81.0; H, 4.87; N, 6.22.

3b: yield: 82%; mp 130-32°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 3H, 4'-OCH_3), 6.94 (d, 2H, 3'-, 5'-H, J = 8.74 Hz), 6.98 (dd, 1H, 5-H, J = 6.5 & 6.67 Hz), 7.18 (d, 1H, 1"-H, J = 16.37 Hz), 7.28 (dd, 1H, 6-H, J = 6.35 & 7.18 Hz), 7.53-7.56 (m, 3H, 7-, 2'-, 6'-H), 7.56 (d, 1H, 2"-H, J = 16.37 Hz), 7.63 (d, 1H, 4-H, J = 8.74 Hz); IR (Nujol) 1630, 1600, 1450 cm^{-1} (C=N and C=C); ^{13}C NMR (75.5 MHz): δ = 163.973 (C-3), 115.345 (C-3a), 115.107 (C-4), 119.950 (C-5), 123.662 (C-6), 109.883 (C-7), 157.398 (C-7a), 128.440 (C-1'), 128.739 (C-2', C-6'), 114.417 (C-3', C-5'), 160.697 (C-4'), 130.819 (C-1"), 134.787 (C-2"), 55.353 (4'-OCH_3); HRMS (m/z): 252.0959 (M^++1, 24.6), 251.0946 (M^+, 100), 250 (26), 236 (20), 220 (17); Anal Calcd. for $C_{16}H_{13}NO_2$: C, 76.49; H, 5.18; N, 5.58. Found: C, 76.10; H, 5.25; N, 5.42.

3c: yield: 84%; mp 162°C; ^1H NMR (DMSO-d_6, 300 MHz): δ 7.12 (dd, 1H, 5-H, J = 6.5 Hz), 7.43 (dd, 1H, 6-H, J = 6.4 & 7.2 Hz), 7.56 (d, 2H, 3'-, 5'-H, J = 8.7 Hz), 7.60 (d, 1H, 7-H, J = 9.0 Hz), 7.68 (d, 1H, 1"-H, J = 16.5 Hz), 7.85 (d, 2H, 2'-, 6'-H, J = 8.5 Hz), 7.86 (d, 1H, 2"-H, J = 16.5 Hz), 8.2 (d, 1H, 4-H, J = 8.7 Hz); IR (Nujol) 1630, 1590, 1460 cm^{-1} (C=N and C=C); ^{13}C NMR (75.5 MHz): δ = 163.397 (C-3), 115.715 (C-3a), 114.598 (C-4), 120.802 (C-5), 124.427 (C-6), 113.240 (C-7), 156.876 (C-7a), 134.693 (C-1'), 129.281 (C-2', C-6'), 128.968 (C-3', C-5'), 133.822 (C-4'), 131.694 (C-1"), 133.339 (C-2"); HRMS (m/z): 255.0445/257.0444 (M^+/M^++2, 100/30.5), 256.0435 (M^++1, 20.3), 238 (7), 227 (20), 192 (60); Anal Calcd. for $C_{15}H_{10}NOCl$: C, 70.45; H, 3.91; N, 5.48. Found: C, 70.52; H, 4.02; N, 5.56.

3d: yield: 83%; mp 138°C; ^1H NMR ($CDCl_3$, 90 MHz): δ 2.25 (s, 3H, 4'-CH3), 6.7-7.7 (m, 10H, Remaining Protons); IR (Nujol) 1625, 1555, 1515, 1450 cm^{-1} (C=N and C=C); HRMS (m/z): 235.1019 (M^+, 100), 220 (20), 181 (7); Anal Calcd. for $C_{16}H_{13}NO$: C, 81.70; H,5.53; N, 5.96. Found: C, 81.60; H, 5.45; N, 5.82.

3e: yield: 82%; mp 189°C; ^1H NMR ($CDCl_3$ + DMSO-d_6, 90 MHz): δ 7.0-7.7 (m, 10 H); IR (Nujol) 1610, 1590, 1455 cm^{-1} (C=N and C=C); ^{13}C NMR (75.5 MHz): δ = 164.410 (C-3), 116.572 (C-3a), 115.368 (C-4), 121.558 (C-5), 125.229 (C-6), 114.072 (C-7), 157.912 (C-7a), 135.812 (C-1'), 132.658 (C-2', C-6'), 130.298 (C-3', C-5'), 123.425 (C-4'), 132.468 (C-1"), 134.216 (C-2"); Anal Calcd. for $C_{15}H_{10}NOBr$: C, 60.20; H, 3.34; N, 4.68. Found: C, 60.36; H, 3.27; N, 4.54.

3f: yield: 83%; mp 126°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3H, 3'-OCH_3), 3.98 (s, 3H, 4'-OCH_3), 6.91 (d, 1H, 5'-H, J = 8.74 Hz), 7.00 (dd, 1H, 5-H, J = 6.5 & 6.67 Hz), 7.13 (d, 1H, 2'-H, J = 2.2 Hz), 7.18 (dd, 1H, 6'-H, J = 8.74 & 2.5 Hz), 7.19 (d, 1H, 1"-H, J = 16.37 Hz), 7.30 (dd,1H, 6-H, J = 6.5 & 6.67 Hz), 7.56 (d, 1H, 7-H, J = 8.74 Hz), 7.57 (d, 1H, 2"-H, J = 16.37 Hz),7.67 (d, 1H, 4-H, J = 8.74 Hz); IR (Nujol) 1612, 1580, 1452 cm^{-1} (C=N and C=C); Anal Calcd. for $C_{17}H_{15}NO_3$: C, 72.59; H, 5.34; N, 4.98. Found: C, 72.46; H, 5.27; N, 4.95.

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