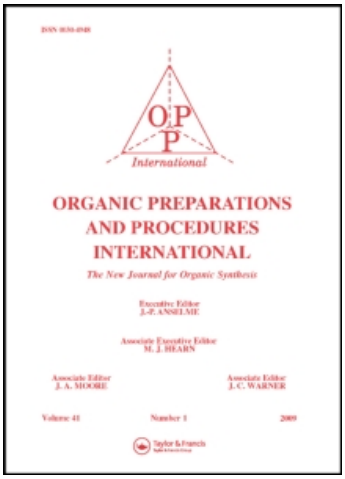

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RUTHENIUM CATALYZED OXIDATION OF HALOINDOLES TO ISATINS

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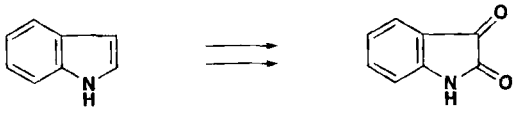
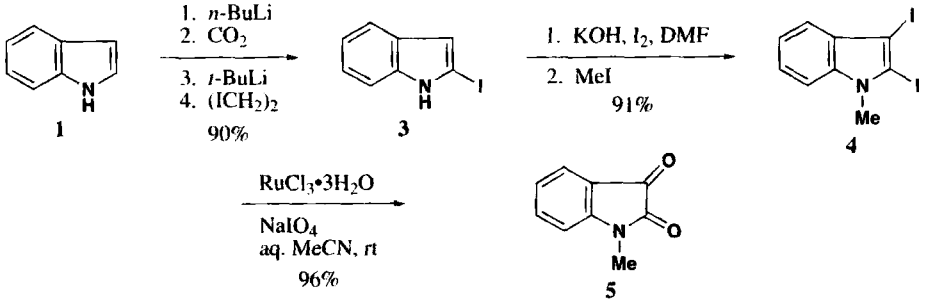
The chemistry and biological activity of isatins (indole-2,3-diones) have seen a resurgence of interest in recent years. For example, isatins have been converted to 3-methylene-2-indolones,[1] 4-quinolinecarboxylic acid inhibitors of prolyl tRNA synthetase,[2] novel spiro oxindoles,[3] indoles enroute to phosphodiesterase inhibitors,[4] analogues of the TMC-95 proteasome inhibitors,[5] and novel 10*H*-indolo[3,2-*b*]quinoline inhibitors of human telomerase.[6] Although there are many synthetic routes to isatins,[7] only one involves the oxidation of indoles (**1**) to isatins (**2**). Parrick and co-workers reported that indoles and 3-bromoindoles are converted to 3,3-dibromooxindoles by treatment with *N*-bromosuccinimide followed by hydrolysis to isatins.[8] In continuation of our interest in the synthesis and chemistry of 2- and 3-haloindoles,[9] we now wish to report a new synthesis of isatins from indoles.



1 **2**

The recent paper by Khan and co-workers[10] describing the ruthenium-catalyzed conversion of vicinal dihaloalkenes to α-diketones suggested that a similar reaction of 2,3-dihaloindoles would lead to isatins.

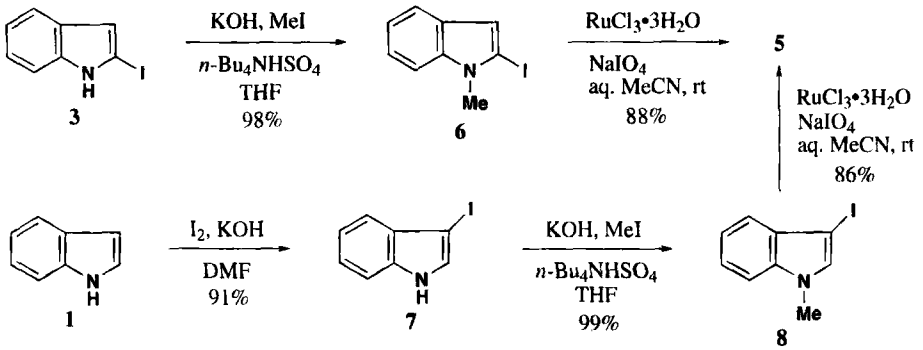
We have previously shown[9b] that indole (**1**) can be transformed to 2,3-diiodo-*N*-methylindole (**4**) in two operations in 82% yield using an extension of Bergman's method.[11] Treatment of **4** with a catalytic amount of ruthenium trichloride in aqueous acetonitrile with sodium periodate as a cooxidant gave *N*-methylisatin (**5**) in 96% yield after recrystallization (*Scheme 1*). The spectral and



Scheme 1

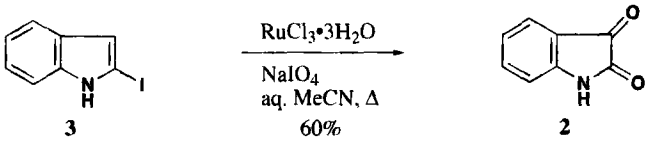
physical properties of **5** agreed with those reported by Bergman by comparison with an authentic sample (IR, NMR, TLC).[12]

The same reaction conditions also transformed both 2- and 3-iodo-*N*-methylindole (**6** and **8**) into *N*-methylisatin (**5**) in 88% and 86% yields, respectively (*Scheme* 2). Unfortunately, the reaction

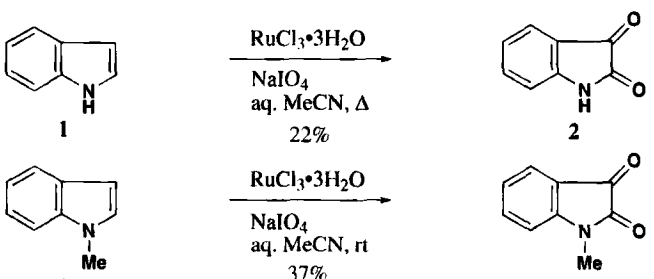


Scheme 2

of 2,3-diiodo-*N*-(phenylsulfonyl)indole[13] under these conditions (reflux) gave no indication of *N*-(phenylsulfonyl)isatin formation. Likewise, 3-iodoindole (**7**) afforded only a trace of isatin. However,



2-iodoindole (**3**) gave isatin (**2**) in 60% yield, identical with a commercial sample. Interestingly, both indole (**1**) and *N*-methylindole (**9**) afforded isatin (**2**) and *N*-methylisatin (**5**), respectively, in modest yields.



In summary, although indoles themselves undergo ruthenium catalyzed oxidation to isatins in low yields, the presence of iodine on the indole 2- and 3-positions greatly facilitates this novel indole to isatin transformation.

EXPERIMENTAL SECTION

Mps were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. ^{1}H NMR spectra were

obtained on a Varian XL-300 Fourier-transform NMR spectrometer (300 MHz) or on a Varian Unitplus spectrometer (500 MHz). ^{13}C NMR were determined on a Varian Unitplus spectrometer. The chemical shifts are reported in δ (ppm) using the δ 7.27 signal of $CHCl_3$ or the δ 2.50 signal of DMSO (^1H NMR) and the δ 77.2 signal of $CDCl_3$ or the δ 39.5 signal of DMSO-d_6 (^{13}C NMR) as internal standards. Flash chromatography was performed using flash silica gel obtained from Selecto Scientific. THF was freshly distilled from sodium/benzophenone. Ruthenium chloride hydrate ($RuCl_3 \cdot xH_2O$) was purchased from Acros Organics and calculated according to the formula $RuCl_3 \cdot 3H_2O$. All other chemicals and reagents were purchased from Aldrich, Acros Organics, or Fisher and used without further purification.

1-Methyl-2,3-diiodoindole (4).- To a mixture of 2-iodoindole (**3**)[11] (0.972 g, 4.00 mmol) and potassium hydroxide (0.560 g, 0.0100 mol) in DMF (20mL) was added dropwise a solution of iodine (1.03 g, 4.06 mmol) in DMF (15 mL). The mixture was stirred for additional 30 min. Methyl iodide (0.500 mL, 8.03 mmol) was added via a syringe along with tetrabutylammonium hydrogen sulfate (50 mg, 0.15 mmol). The reaction mixture was stirred for an additional 1.5 h, then poured into aqueous sodium thiosulfate solution and extracted with ethyl acetate. The organic layer was washed with water and dried over magnesium sulfate. The product was obtained after removal of the solvent as a solid (1.39 g, 91%); mp 64-65° (*lit.*[14] mp 76-78°); ^1H NMR ($CDCl_3$) δ 7.41 (m, 1H), 7.29 (m, 1H), 7.23-7.14 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 137.9, 130.9, 122.5, 120.6, 120.3, 110.9, 99.7, 71.6, 35.9.

***N*-Methylisatin (5).**- To a mixture of 1-methyl-2,3-diiodoindole (**4**) (77 mg, 0.20 mmol) and a catalytic amount of $RuCl_3 \cdot 3H_2O$ (Acros) (3.7 mg) in acetonitrile-water (5:1) (12 mL) cooled in an ice bath was added sodium periodate (0.13 g, 0.60 mmol). The resulting mixture was then stirred at room temperature for 8 h at which point TLC showed the completion of the reaction. The reaction mixture was extracted with ethyl acetate (3 x 20 mL) and washed several times with water. The organic layer was dried over magnesium sulfate and a dark red solid was obtained after removal of solvent in vacuo. The crude product was recrystallized from aqueous ethanol to give **5** as orange red needles (31 mg, 96%); mp 128-130° (*lit.*[12] mp 126-128°); ^1H NMR ($CDCl_3$) δ 7.62 (m, 2H), 7.15 (t, 1H, J = 8.0 Hz), 6.91 (d, 1H, J = 8.5 Hz), 3.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 183.5, 158.2, 151.4, 138.2, 124.3, 123.2, 117.4, 110.6, 26.0; IR (film) ν 1728, 1606, 1467, 1367, 1322, 1089, 750 cm^{-1}. This sample was identical by NMR, IR, and TLC to a sample kindly provided by Bergman.[12]

1-Methyl-2-iodoindole (6).- A mixture of 2-iodoindole (**3**) (1.95 g, 8.02 mmol), potassium hydroxide (0.900 g, 0.0161 mol), methyl iodide (1.00 mL, 0.0161 mmol) and tetrabutylammonium hydrogen sulfate (0.135 g, 0.400 mmol) in THF (60 mL) was stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate, washed with water, and dried over magnesium sulfate. The crude solid after removal of solvent was recrystalized from ethyl ether/hexane to yield **6** as a white solid (2.01 g, 98%); mp 75° (*lit.*[11] mp 76°); ^1H NMR (DMSO-d_6) δ 7.47 (m, 2H), 7.11 (m, 1H), 7.01 (m, 1H), 6.78 (s, 1H), 3.74 (s, 3H).

3-Iodoindole (7).- This was prepared by a modification of the literature procedure.[15] To a solution of indole (1.00 g, 8.55 mmol) in DMF (10 mL) was added potassium hydroxide (1.20 g, 21.4 mmol) (crushed pellets). A solution of iodine (2.28 g, 8.98 mmol) in DMF (5 mL) was added in dropwise.

The reaction mixture was poured into an aqueous solution of sodium thiosulfate and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water and dried over magnesium sulfate. The residue after removal of the solvent in vacuo was purified by flash chromatography (EtOAc/hexane 30:70) to yield the desired product as orange-yellow solid (1.90 g, 91%): mp 66° (dec.) (*lit.*[15] mp 76°); ^{1}H NMR ($CDCl_3$) δ 8.4 (broad, s, 1H), 7.48 (m, 1H), 7.39 (m, 1H), 7.31 (d, 1H, J = 2.0 Hz), 7.28-7.21 (m, 2H).

1-Methyl-3-iodoindole (8).- A mixture of 3-iodoindole (0.500 g, 2.06 mmol), potassium hydroxide (0.235 g, 4.20 mmol), methyl iodide (0.26 mL, 4.2 mmol) and tetabutylammonium hydrogen sulfate (35 mg, 0.10 mmol) in THF (20 mL) was stirred at room temperature for 3 h. The reaction mixture was extracted with ethyl acetate, washed with water, and dried over magnesium sulfate. The desired product was obtained as a brownish oil (0.526 g, 99%) after removal of the solvent; ^{1}H NMR (DMSO-d_6) δ 7.55 (s, 1H), 7.47 (m, 1H), 7.29-7.13 (m, 3H), 3.81 (s, 3H); HRMS Calcd for C_9H_8IN: 256.9702; found: 256.9707. The literature also reports this compound as an oil.[15]

Isatin (2).- A mixture of 2-iodoindole (**3**) (0.100 g, 0.412 mmol), sodium periodate (0.260 g, 1.21 mmol), ruthenium chloride hydrate (7.5 mg, 0.0287 mmol) and acetonitrile/water (5:1) (10 mL) was heaated to reflux for 2 h. The mixture was poured into water and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water and dried over magnesium sulfate. The residue after removal of solvent was purified by flash chromatography (ethyl acetate/hexane 50/50) to afford **2** (0.036 g, 60%) as orange needles; mp 200-201° (*lit.*[16] mp 200°); ^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 7.59 (m, 1H), 7.50 (m, 1H), 7.07 (m, 1H), 6.91 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 184.4, 159.4, 150.7, 138.4, 124.7, 122.8, 117.8, 112.2. This sample was identical by NMR, IR, and TLC to a commercial sample of isatin (Aldrich).

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