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DECARBOXYLATIVE BROMINATION OF INDOLE-2,3-DICARBOXYLIC ACIDS USING OXONE® OR CAN IN THE PRESENCE OF LITHIUM BROMIDE

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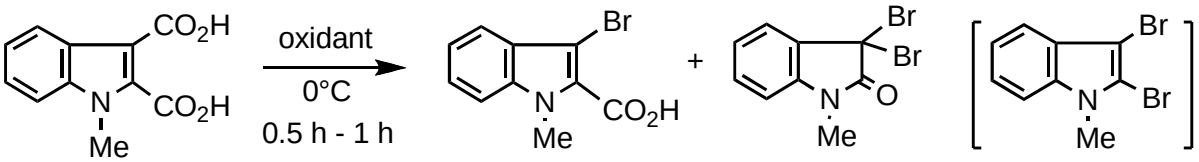
Abstract – The treatment of 1-methylindole-2,3-dicarboxylic acid with Oxone® and lithium bromide produced 3,3-dibromo-1-methyloxindole. However, the reaction of 1-benzenesulfonylindole-2,3-dicarboxylic acid with Oxone® and lithium bromide afforded 1-benzenesulfonyl-2,3-dibromoindole. In a similar manner, 2,3,5,6-tetrabromoindole was synthesized from 1-benzenesulfonyl-5,6-dibromoindole-2,3-dicarboxylic acid.

Bromoarenes are an important class of compounds due to their conversion to other functionalities by the Heck-type reaction in the presence of a palladium catalyst, etc. The bromination of activated arenes is usually performed by conventional bromination methods typically using toxic bromine. Commercial available Oxone® ($2KHSO_5 \cdot KHSO \cdot K_2SO_4$) is an inexpensive, and stable oxidant and in the presence of sodium bromide or potassium bromide, Oxone® can be used as an efficient bromination reagent for activated arenes.[1] The decarboxylative bromination of aromatic carboxylic acids using Oxone® and sodium bromide is also a useful method,[2] but there is no report about the decarboxylative bromination of indolecarboxylic acids. Bromoindole alkaloids have also been isolated as secondary metabolites of marine organisms, such as sponges, tunicates, etc., and are promising sources of new biologically active molecules.[3] 2,3,5,6-Tetrabromoindole[4,5] having antibacterial and antitumor activities was isolated and synthesized by Castillo.[6] 3,6-Dibromoindole also was isolated.[7] We have shown that the dimethyl indole-2,3-dicarboxylates and indole-2,3-dicarboxylic anhydrides are useful synthons in the synthesis of pratosine,[8] hippadine,[8] murrayaquinone-A,[9] ellipticine,[10-12] olivacine,[13] caulersin[14] and cryptosanguinolentine.[15] In this report we describe the synthesis of bromoindoles by the decarboxylative bromination of indole-2,3-dicarboxylic acids using a combination of Oxone® or CAN (ceric ammonium nitrate)[16] and lithium bromide

The reaction of 1-methylindole-2,3-dicarboxylic acid (**1a**)[17] with 0.5 equivalent of Oxone® ($2KHSO_5 \cdot$

KHSO · K_2SO_4)[2] in the presence of 5 equivalents of sodium bromide and 1 equivalent of sodium carbonate in MeOH-H_2O (1 : 1) gave 3-bromoindole-2-carboxylic acid (**2a**)[18] in 44% yield, but the treatment of **1a** with Oxone® in the presence of lithium bromide and lithium carbonate afforded **2a** in 62% yield. (Entries 1, 2) However, when the reaction of **1a** with 2 equivalents of Oxone® in the presence of 10 equivalents of lithium bromide and 2 equivalents of lithium carbonate, 3,3-dibromooxindole (**3a**)[19] was obtained in 36% yield instead of **2a**, but the 2,3-dibromoindole (**4a**) was not isolated. (Entry 3) **1a** was treated with 1 equivalent or 3 equivalents of CAN in the presence of lithium bromide in acetonitrile to afford a mixture of **2a** and **3a** in 51-69% and 20-34% yields, respectively. (Entries 4, 5) (Table 1)



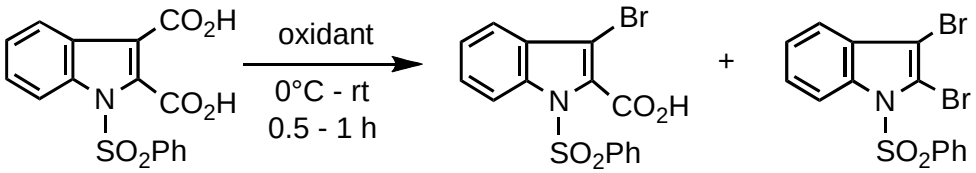
1a **2a** **3a** **4a**

Scheme 1

Table 1

Entry	Oxidant	MBr	Base	Solvent	Yield(%) 2a	3a
1	Oxone® (0.5 eq)	NaBr (5 eq)[1)]	Na_2CO_3 (1 eq)	MeOH-H_2O	44	-
2	Oxone® (0.5 eq)	LiBr (5 eq)	Li_2CO_3 (1 eq)	MeOH-H_2O	62	-
3	Oxone® (2 eq)	LiBr (10 eq)	Li_2CO_3 (2 eq)	MeOH-H_2O	-	36
4	CAN (1 eq)	LiBr (1 eq)	-	CH_3CN	69	20
5	CAN (3 eq)	LiBr (3 eq)	-	CH_3CN	51	34

The treatment of 1-benzenesulfonylindole-2,3-dicarboxylic acid (**1b**)[20] with 1 equivalent of Oxone® in the presence of lithium bromide and lithium carbonate gave a mixture of 3-bromoindole-2-carboxylic acid (**2b**) and 2,3-dibromoindole (**4b**)[21] in 26% or 57% yields, respectively, but **1b** was reacted with 2 equivalents of Oxone® to provide **4b** in 88% instead of the corresponding 3,3-dibromooxindole (Entries 1, 2) However, treatment of **1b** with CAN led to a mixture of **2b** and **4b** in low yields, respectively. (Entries 3, 4) (Table 2)



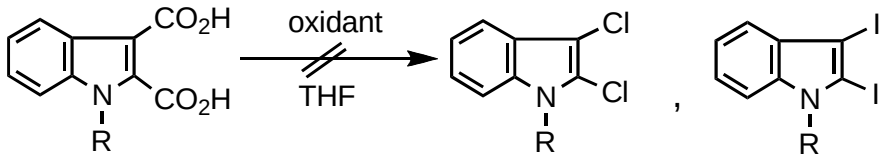
1b **2b** **4b**

Scheme 2

Table 2

Entry	Oxidant	LiBr	Base	Solvent	Yield(%) **2b**	**4b**
1	Oxone® (1 eq)	5 eq	Li_2CO_3 (1 eq)	MeOH-H_2O	26	57
2	Oxone® (2 eq)	10 eq	Li_2CO_3 (2 eq)	MeOH-H_2O	-	88
3	CAN (1 eq)	1 eq	-	CH_3CN	16	3
4	CAN (3 eq)	3 eq	-	CH_3CN	13	19

Next, we evaluated the syntheses of the 2,3-dichloroindoles (**5**) or 2,3-diiodoindoles (**6**) by the reaction of **1** with Oxone® in the presence of lithium chloride or lithium iodide. The reaction of 1-methylindole-2,3-dicarboxylic acid (**1a**) or 1-benzenesulfonylindole-2,3-dicarboxylic acid (**1b**) with 2 equivalents of Oxone® and lithium chloride or 3 equivalents of CAN and lithium chloride resulted in a complex mixture. When **1a** or **1b** was treated with Oxone® or CAN in the presence of lithium iodide, the corresponding 2,3-diiodoindoles (**6**) were also not isolated.

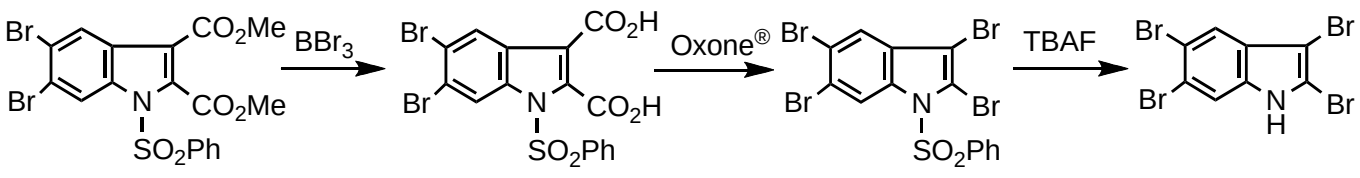


1a,b **5** **6**

a: R = Me, **b**: R = SO_2Ph

Scheme 3

The treatment of dimethyl 1-benzenesulfonyl-5,6-dibromoindole-2,3-dicarboxylate (**7**)[22] with boron tribromide gave the corresponding dicarboxylic acid (**8**) (92%), which was treated with Oxone® (2 equivalents) in the presence of lithium bromide and lithium carbonate to provide 1-benzenesulfonyl-2,3,5,6-tetrabromoindole (**9**) in 66% yield. **9** could be converted to 2,3,5,6-tetrabromoindole (**10**)[6] by treatment with tetrabutylammonium fluoride in THF in 92% yield.



7 **8** **9** **10**

Scheme 4

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EXPERIMENTAL

Melting points were determined using a Yanagimoto micromelting point apparatus and are uncorrected. The ^{1}H-NMR spectra were determined by a JEOL JNM-GSX 270 spectrometer using tetramethylsilane as the internal standard. The IR spectra were recorded by a JASCO FT/IR-7000 spectrophotometer. The high MS were recorded using a JOEL JMS-HX100 spectrometer. Column chromatography was performed on E. Merck silica gel 60 (70-230 mesh or 230-400 mesh).

General Procedure: Reaction of Indole-2,3-dicarboxylic Acid (1) with Oxone® in the presence of a lithium halide and lithium carbonate

Indole-2,3-dicarboxylic acid (**1**)(1 mmol) was added to the mixture of Oxone®, lithium halide, and lithium carbonate in MeOH-H_2O (1 : 1). The mixture was then stirred at room temperature. A 2 % sodium thiosulfate aqueous solution was added to the reaction mixture and the mixture was extracted with CH_2Cl_2, washed with water, and dried over Na_2SO_4. The extracts were concentrated under reduced pressure to afford a residue, which was purified by column chromatography.

General Procedure: Reaction of 1 with CAN in the presence of a lithium halide

CAN was added to the mixture of indole-2,3-dicarboxylic acid (**1**) (1 mmol) and lithium halide in MeCN. The mixture was then stirred at room temperature. A 2 % sodium thiosulfate aqueous solution was added to the reaction mixture and the aqueous mixture was extracted with CH_2Cl_2, washed with water, and dried over Na_2SO_4. The extracts were concentrated under reduced pressure to afford a residue, which was purified by column chromatography.

3-Bromo-1-methylindole-2-carboxylic acid (2a); mp 184-186 °C (lit.,[18] mp 180 °C (dec). IR (KBr) ν: 1671 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.99 (3H, s, CH_3), 7.22 (1H, t, J = 8 Hz, H-5 or H-6), 7.40 (1H, t, J = 8 Hz, H-6 or H-5), 7.54 (1H, d, J = 8 Hz, H-4 or H-7), 7.62 (1H, d, J = 8 Hz, H-7 or H-4).

3,3-Dibromo-1-methyloxindole (3a); mp 202-204 °C (EtOAc) (lit.,[19] mp 204-205 °C). IR ($CHCl_3$) ν: 1737 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.26 (3H, s, CH_3), 6.86 (1H, d, J = 8 Hz, H-4 or H-7), 7.17 (1H, dt, J = 8, 1.5 Hz, H-5 or H-6), 7.34 (1H, dt, J = 8, 1.5 Hz, H-6 or H-5), 7.62 (1H, dd, J = 8, 1.5 Hz, H-7 or H-4). ^{13}C-NMR (DMSO-d_6) δ: 169.16, 139.64, 131.87, 130.37, 125.38, 124.05, 110.08, 45.28, 27.03. HRMS (EI) *m/z*: Calcd for $C_9H_7NOBr_2$: 302.8895. Found: 302.8883.

1-Benzenesulfonyl-3-bromoindole-2-carboxylic acid (2b); mp 219-222 °C (EtOAc). IR (Nujol) ν: 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.24-7.36 (3H, m, aromatic protons), 7.50-7.68 (3H, m, aromatic protons), 7.91 (1H, dd, J = 8, 1.5 Hz, aromatic protons), 8.25-8.32 (2H, m, aromatic protons). HRMS (EI) *m/z*: Calcd for $C_{15}H_{11}NSO_4Br_2S$: 379.9592. Found: 379.9602.

1-Benzenesulfonyl-2,3-dibromoindole (4b); mp 143 °C (lit.,[21] mp 141-143 °C). ^{1}H-NMR ($CDCl_3$) δ: 7.22-7.40 (5H, m, aromatic protons), 7.46-7.54 (1H, m, aromatic protons), 7.78-7.84 (2H, m, aromatic

protons), 8.19-8.25 (1H, m, aromatic protons).

2,3,5,6-Tetrabromoindole (10)

To a solution of dimethyl 1-benzenesulfonyl-5,6-dibromoindole-2,3-dicarboxylate (**7**)[22] (531 mg, 1 mmol) in toluene (10 mL) was added 1M boron tribromide in a CH_2Cl_2 solution (3 mL). The mixture was then stirred at room temperature overnight. Water was added to reaction mixture and the precipitate was collected by filtration and washed with water, then with *n*-hexane. The 1-benzenesulfonyl-5,6-dibromoindole-2,3-dicarboxylic acid (**8**) (464 mg, 92%) was used without purification.

8; IR (KBr) ν: 1763, 1692 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 7.65-7.82 (3H, m, aromatic protons), 8.10-8.15 (2H, m, aromatic protons), 8.27 (1H, s, H-4 or H-7), 8.33 (1H, s, H-7 or H-4).

1-Benzenesulfonyl-5,6-dibromoindole-2,3-dicarboxylic acid (**8**) (25 mg, 0.05 mmol) was added to the mixture of Oxone® (62 mg, 0.1 mmol), lithium bromide (47 mg, 0.5 mmol), and lithium carbonate (7 mg, 0.1 mmol) in MeOH-H_2O (1 : 1) (2 mL), then the mixture was stirred at room temperature overnight. A 2 % sodium thiosulfate aqueous solution was added to the reaction mixture which was then extracted with $CHCl_3$, washed with water, and dried over Na_2SO_4. The extracts were concentrated under reduced pressure to afford a residue, which was purified by column chromatography (*n*-hexane : EtOAc = 3 : 1) to give 1-benzenesulfonyl-2,3,5,6-tetrabromoindole (**9**) (19 mg, 66%).

9; mp 158-161 °C ($CHCl_3$), ^{1}H-NMR ($CDCl_3$) δ: 7.41-7.60 (3H, m, aromatic protons), 7.64 (1H, s, H-4), 7.80-7.86 (2H, m, aromatic protons), 8.56 (1H, s, H-7).

A 1M solution of tetrabutylammonium fluoride in THF (0.04 mL) was added to a mixture of 1-benzenesulfonyl-2,3,5,6-tetrabromoindole (**9**) (11 mg, 0.02 mmol) in THF (1 mL) at -20 °C under argon and the reaction mixture was stirred for 1 h at the same temperature. Hydrochloric acid (2 %) was added to the mixture and then extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4, then concentrated under reduced pressure to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 3:1) to give the 2,3,5,6-tetrabromoindole (**10**)[4] (8 mg, 92%), mp 153-154 °C (lit.,[4] mp 152.5-154 °C, lit.,[6] mp 153-154 °C), ^{1}H-NMR ($CDCl_3$) δ: 7.61 (1H, s, H-4 or H-7), 7.76 (1H, s, H-7 or H-4), 8.38 (1H, br s, NH).

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