# Hypervalent Iodine(III) Mediated Decarboxylative Halogenation of Indolecarboxylic Acids for the Synthesis of Haloindole Derivatives

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**Abstract:** The treatment of 1-methylindole-2,3-dicarboxylic acid with hypervalent iodine(III) reagent, phenyliodine diacetate (PIDA), in the presence of lithium bromide gave 1-methyl-3,3-dibromooxindole. However, the reaction of 1-(phenylsulfonyl)indole-2,3-dicarboxylic acid with PIDA in the presence of lithium bromide afforded 2,3-dibromo-1-(phenylsulfonyl)indole. In a similar manner, the 2,3-dichloro- and 2,3-diiodo-indole derivatives were obtained by the reaction of the indole-2,3-dicarboxylic acids with PIDA in the presence of lithium chloride and iodide.

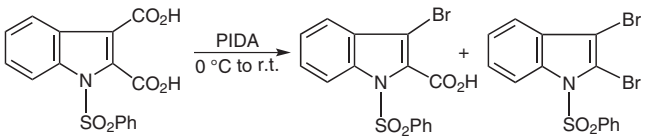
**Key words:** indolecarboxylic acid, decarboxylation, bromination, chlorination, iodation

The Hunsdiecker reaction, the reaction of heavy-metal salt of carboxylic acids with halogens to give organic halides, is an example of classical decarboxylative halogenation reaction.[1] Thus the decarboxylative halogenation that can provide halogenated organic compounds from carboxylic acids, an important class of intermediates, by simple chemical transformation is very attractive. Recently, several Hunsdiecker-type reactions have been investigated using the various reagent conditions, especially using hypervalent iodine compounds in the point of green chemistry.[2] Camps reported that 2- and 4-nitrobenzoic acids having electron-withdrawing substituent could be converted into the corresponding bromonitrobenzenes in moderate yield by decarboxylative bromination using phenyliodine diacetate (PIDA) and bromine under irradiation, but in the case of 2- and 4-methoxybenzoic acids, possessing a electron-donating substituent, were recovered and this result shows that the conversion of electron-rich aromatic carboxylic acid into the corresponding bromobenzene is quite difficult.[3] Although the decarboxylative halogenation is an attractive method for the synthesis of simple halogenated organic compounds, the application of the Hunsdiecker-type reactions for the synthesis of natural products or bioactive compounds is still limited.[3,4]

Bromoindole alkaloids have been isolated as the secondary metabolites of marine organisms, such as sponges, tunicates, etc., and are promising sources of new biologically active molecules.[5] 2,3,6-Tribromoindole,[6] 2,3,5,6-tetrabromoindole,[7] the polybromo(bisindoles),[8] and bromochloroindoles[9] were isolated. The synthesis of the bromoindoles is usually performed by the direct bromination of indoles using bromine, pyridinium tribromide, *N*-bromosuccinimide, etc., but the yields or the selectivity are not satisfactory in general. There is no such report of indolecarboxylic acids except for the synthesis of the 2,3-diiodoindoles by the decarboxylative iodination of indole-2-carboxylic acids, but in the case of indole-2-carboxylic acids without having an electron-donating substituent, the yield of the 2,3-diiodoindoles are low.[10] Recently, we reported the synthesis of the 2,3-dibromoindoles by the decarboxylative bromination of indole-2,3-dicarboxylic acids by using Oxone® and lithium bromide, but 2,3-dichloro- or 2,3-diiodo-indoles were not obtained.[11]

We now investigated the Hunsdiecker-type decarboxylative halogenation of 1-substituted indole-2,3-dicarboxylic acids **1** utilizing hypervalent iodine reagent, by the way the effective strategy for halogenation because hypervalent iodine reagents have low toxicity relative to heavy metals and are readily available and their reactivities are similar to those of heavy metals.[12]

The reaction of 1-(phenylsulfonyl)indole-2,3-dicarboxylic acid (**1a**)[13] with 3 equivalents of PIDA[14] in the presence of the same equivalents of lithium bromide in THF gave a mixture of 3-bromoindole-2-carboxylic acid (**2a**) and 2,3-dibromoindole (**3a**)[15] in 36% and 35% yields, respectively, but the treatment of **1a** with PIDA (4 equiv) afforded **3a** in 86% yield (Table 1, entries 1, 2). However, when the reaction of **1a** with PIDA was carried out using potassium bromide instead of lithium bromide, 5 equivalents of PIDA or $CH_2Cl_2$ as the solvent, the yields of **3a** were relative low (33–72%, Table 1, entries 3–5, Scheme 1).




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

**Scheme 1** The reaction of **1a** with PIDA in the presence of lithium bromide

The reaction of 1-methylindole-2,3-dicarboxylic acid (**1b**)[16] with 1 equiv or 2 equiv of PIDA in the presence of the same equivalents of lithium bromide in THF gave 3-bromoindole-2-carboxylic acid (**2b**)[17] in 57% or 74%

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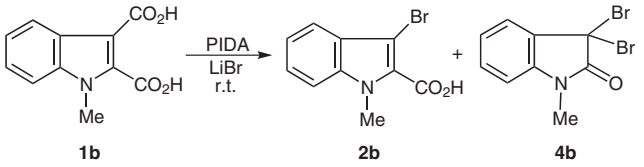
**Table 1** Synthesis of **2a** and **3a**

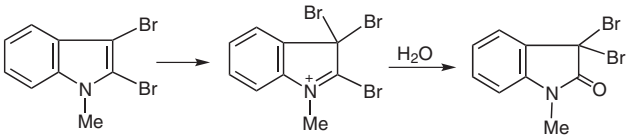
| Entry | PIDA (equiv) | MBr | Solvent | Time (h) | Yield of **2a** (%) | Yield of **3a** (%) |
|---|---|---|---|---|---|---|
| 1 | 3 | LiBr | THF | 51 | 36 | 35 |
| 2 | 4 | LiBr | THF | 2 | – | 86 |
| 3 | 4 | KBr | THF | 22 | 6 | 72 |
| 4 | 5 | LiBr | THF | 3 | – | 71 |
| 5 | 5 | LiBr | $CH_2Cl_2$ | 0.5 | – | 33 |




**Scheme 2** The reaction of **1b** with PIDA in the presence of lithium bromide

**Table 2** Synthesis of **2b** and **4b**

| Entry | PIDA (equiv) | Solvent | Time (h) | Yield of **2b** (%) | Yield of **4b** (%) |
|---|---|---|---|---|---|
| 1 | 1 | THF | 1 | 57 | – |
| 2 | 2 | THF | 2 | 74 | – |
| 3 | 3 | THF | 1 | – | 78 |
| 4 | 3 | $CH_2Cl_2$ | 0.5 | – | 73 |




**Scheme 3** Plausible reaction mechanism leading to **4b**

**Table 3** Synthesis of **3** and **4b** from Indolecarboxylic Acids **6** and **7**

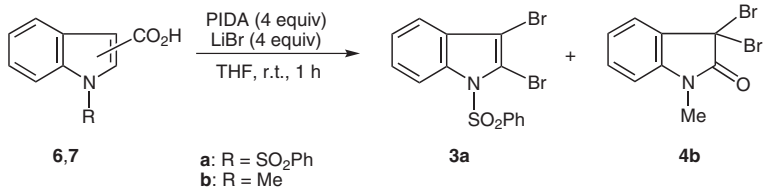
| Entry | Compd | $CO_2H$ | R | Yield of **3** (%) | Yield of **4b** (%) |
|---|---|---|---|---|---|
| 1 | **6a** | 2- | $SO_2Ph$ | 83 | – |
| 2 | **7a** | 3- | $SO_2Ph$ | 81 | – |
| 3 | **6b** | 2- | Me | – | 80 |
| 4 | **7b** | 3- | Me | – | 80 |

yields, respectively (Table 2, entries 1, 2). When the reaction of **1b** with 3 equivalents of PIDA was examined, the corresponding 2,3-dibromoindole (**3b**), the desired product was not isolated and 3,3-dibromo-1-methyloxindole (**4b**)[18] was obtained as the sole product in 78% yield (entry 3). In addition, the reaction of **1b** with 3 equivalents of PIDA in $CH_2Cl_2$ instead of THF also afforded **4b** in slightly lower yield (73%, entry 4). When 3-bromoindole-2-carboxylic acid (**2b**) was treated with with PIDA (2 equiv) and lithium bromide in THF at room temperature (30 min), **4b** was obtained in 90% yield (Scheme 2).

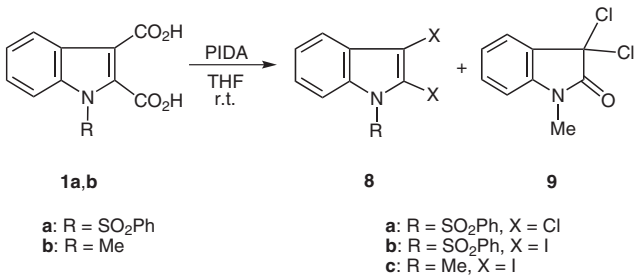
One possible explanation for the formation of 3,3-dibromo-1-methyloxindole (**4b**) is envisaged as shown in Scheme 3. The bromination of 1-methyl-2,3-dibromoindole (**3b**), which would obtained after the second Hunsdiecker-type decarboxylative bromination of **1b**, lead to intermediate **5**. Treatment of **5** with water by work-up provides **4b**. The absence of 3,3-dibromo-1-(phenylsulfonyl)oxindole on the reaction with **1a**, possessing electron-withdrawing N-substituent in Table 1 may support this explanation. Although the detailed reaction mechanism is still not clear, the dibromooxindole derivatives could be also potentially attractive synthons in indole alkaloid syntheses.

The reaction of 1-(phenylsulfonyl)indole-2-carboxylic acid (**6a**) or 1-(phenylsulfonyl)indole-3-carboxylic acid (**7a**) with 4 equivalents of PIDA in the presence of the same equivalents of lithium bromide in THF gave **3a** in 81–83% yields (Table 3, entries 1, 2), but from 1-methylindole-2-carboxylic acid (**6b**) or 1-methylindole-3-carboxylic acid (**7b**), **4b** was isolated in 80% yields (entries 3, 4). The same results were obtained with the reaction of **1** with PIDA and lithium bromide (Scheme 4).

Next, we examined the reactivity of **1** toward lithium chloride or iodide to synthesize the dichloro- or diiodoindoles **8** (Table 4). The reaction of 1-(phenylsulfonyl) indole-2,3-dicarboxylic acid (**1a**) with less than 4 equivalents of PIDA in the presence of lithium chloride in THF gave 2,3-dichloroindole (**8a**) in low yield, but the treatment of **1a** with PIDA (6 equiv) afforded **8a** in 80% yield (entry 1). 2,3-Diiodo-1-(phenylsulfonyl)indole (**8b**) was not isolated by the treatment of **1a** with 6 equivalents of PIDA in the presence of lithium iodide in THF, but in a mixture of 2,2,2-trifluoroethanol and $CH_2Cl_2$ (1:1) as a solvent instead of THF, **8b**[19] was obtained in 89% yield (entry 2). The reaction of **1b** with PIDA (4 equiv) in the presence of lithium chloride gave 3,3-dichlorooxindole **9**[20] in 77% yield, and 2,3-diiodo-1-methylindole (**8c**)[21] was isolated in 87% yield in the presence of lithium iodide (Table 4, entries 3, 4; Scheme 5).




**Scheme 4** The reaction of **6** and **7** with PIDA in the presence of lithium bromide




**1a,b** **8** **9**

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

**a**: R = $SO_2Ph$, X = Cl
**b**: R = $SO_2Ph$, X = I
**c**: R = Me, X = I

**Scheme 5** The reaction of **1** with PIDA in the presence of lithium chloride or iodide

**Table 4** Synthesis of **8** and **9**[22]

| Entry | R | PIDA (equiv) | LiX | Time (h) | Yield of **8** (%) | Yield of **9** (%) |
|---|---|---|---|---|---|---|
| 1 | $SO_2Ph$ | 6 | LiCl | 6 | 80 | – |
| 2 | $SO_2Ph$ | 5 | LiI | 3 | 89[a] | – |
| 3 | Me | 4 | LiCl | 6 | – | 77 |
| 4 | Me | 4 | LiI | 1.5 | 87 | – |

[a] 2,2,2-Trifluoroethanol and $CH_2Cl_2$ (1:1) was used as a solvent instead of THF.

In conclusion, we demonstrated the decarboxylative halogenation of indolecarboxylic acid derivatives using the Hunsdiecker-type reaction. The exciting result obtained with the reaction of the indole-2,3-dicarboxylic acids **1** with PIDA in the presence of lithium halide prompted us to extend our procedure to the selective synthesis of indole alkaloids.

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(22) **Typical Procedure for the Decarboxylative Halogenation of Indole-2,3-dicarboxylic Acid(1) with PIDA in the Presence of Lithium Halide**
To a mixture of PIDA and lithium halide in THF (10 mL) was added indolecarboxylic acids **1**, **6**, **7** (1 mmol) at r.t., and then the reaction mixture was stirred. $H_2O$ was added to the reaction mixture, and the mixture was extracted with $CH_2Cl_2$. The combined extracts were washed with 2–3% $Na_2S_2O_3$ solution, then $H_2O$, and dried over $Na_2SO_4$. The extracts were concentrated under reduced pressure to give a solid, which was purified by column chromatography on silica gel to afford the 3-halogenoindole-2-carboxylic acids(**2**), 2,3-dihalogenoindoles **3**, **8**, and 3,3-dihalogenooxindoles **4**, **9**.
**1-Phenylsulfonyl-3-bromoindole-2-carboxylic Acid (2a)**
Mp 124–125 °C. IR (mull): ν = 2856, 2585, 1697 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 7.24–7.36 (3 H, m), 7.50–7.68 (3 H, m), 7.91 (1 H, dd, *J* = 8.0, 1.5 Hz), 8.25–8.32 (2 H, m). HRMS (EI): *m/z* calcd for $C_{15}H_{11}NSO_4Br_2S$: 379.9592; found: 379.9602.
**1-Phenylsulfonyl-2,3-dibromoindole (3a)**
Mp 143 °C (lit.[15] mp 141–143 °C). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.22–7.40 (5 H, m), 7.46–7.54 (1 H, m), 7.78–7.84 (2 H, m), 8.19–8.25 (1 H, m).
**3-Bromo-1-methylindole-2-carboxylic Acid (2b)**
Mp 184–186 °C [lit.[17] mp 180 °C (dec)]. IR (KBr): ν = 1671 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 3.99 (3 H, s, $CH_3$), 7.22 (1 H, t, *J* = 8.0 Hz, H-5 or H-6), 7.40 (1 H, t, *J* = 8.0 Hz, H-6 or H-5), 7.54 (1 H, d, *J* = 8.0 Hz, H-4 or H-7), 7.62 (1 H, d, *J* = 8.0 Hz, H-7 or H-4).

**3,3-Dibromo-1-methyloxindole (4b)**
Mp 202–204 °C (lit.[18] mp 204–205 °C). IR ($CHCl_3$): ν = 1737 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 3.26 (3 H, s, $CH_3$), 6.86 (1 H, d, *J* = 8.0 Hz, H-4 or H-7), 7.17 (1 H, dt, *J* = 8.0, 1.5 Hz, H-5 or H-6), 7.34 (1 H, dt, *J* = 8.0, 1.5 Hz, H-6 or H-5), 7.62 (1 H, dd, *J* = 8.0, 1.5 Hz, H-7 or H-4). $^{13}C$ NMR (100 MHz, 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-Phenylsulfonyl-2,3-dichloroindole (8a)**
Mp 122 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.30–7.63 (6 H, m), 7.84–7.92 (2 H, m), 8.28 (1 H, br d, *J* = 8.0 Hz, H-7 or H-4). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 137.59, 134.70, 134.40, 129.30, 126.94, 126.54, 126.14, 124.57, 121.24, 118.15, 114.98, 113.78. HRMS (EI): *m/z* calcd for $C_{14}H_9NO_2Cl_2S$: 324.9677; found: 324.9737.

**1-Phenylsulfonyl-2,3-diiodoindole (8b)**
Mp 165–167 °C (lit.[19] mp 166–167 °C). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.25–7.60 (6 H, m), 7.90 (2 H, br d, *J* = 8.0 Hz), 8.28 (1 H, br d, *J* = 8.0 Hz, H-7).

**2,3-Diiodo-1-methylindole (8c)**
Mp 76–77 °C (lit.[20] mp 76–78 °C). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 3.89 (3 H, s, $CH_3$), 7.10–7.42 (4 H, m). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 138.11, 131.15, 122.71, 120.80, 120.50, 111.06, 99.78, 71.72, 36.09. HRMS (EI): *m/z* calcd for $C_9H_7NI_2$: 382.8668; found: 382.8671.

**3,3-Dichloro-1-methyloxindole (9)**
Mp 144–147 °C (lit.[21] 143 °C). IR (KBr): ν = 1740 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 3.25 (3 H, s, $CH_3$), 6.85 (1 H, d, *J* = 8.0 Hz, H-4 or H-7), 7.17 (1 H, t, *J* = 8.0 Hz, H-5 or H-6), 7.39 (1 H, t, *J* = 8.0, 1.5 Hz, H-6 or H-5), 7.61 (1 H, d, *J* = 8.0 Hz, H-7 or H-4). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 168.80, 140.58, 131.85, 129.16, 125.13, 124.70, 124.14, 109.08, 26.98.