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# SELECTIVE HALOGENATION OF 4-OXO-4,5,6,7-TETRAHYDROINDOLES TO 5-HALO-4-OXO-4,5,6,7-TETRAHYDROINDOLES WITH COPPER(II) HALIDES

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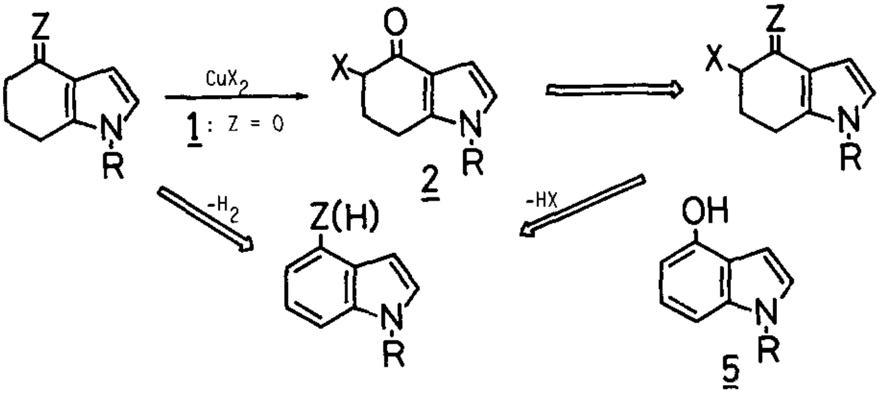
Abstract —— Halogenation of 4-oxo-4,5,6,7-tetrahydroindoles with copper(II) bromide or copper(II) chloride gave selectively 5-halo-4-oxo-4,5,6,7-tetrahydroindoles, which were easily transformed to 4-hydroxyindoles by the action of lithium halide/lithium carbonate in dimethylformamide.

One of attractive synthetic routes to 4-substituted indoles is to use 4-oxo-4,5,6,7-tetrahydroindole (1) as a key intermediate. The synthon of indole 1 has, however, been limited to use, because oxidative aromatization of the cyclohexene skeleton of type 1 compound requires drastic reaction conditions and is often fruitless.[1,2,4] It is thought that a practical step solving these problems is to oxidize 1 into 5-halo-4-oxo-4,5,6,7-tetrahydroindoles (2) prior to transformation of the carbonyl group of 1 to various functionalities. We report here that the halogenation of 1 to 2 was attained by the use of copper(II) halides and shows the facile synthesis of 4-hydroxyindoles (5) from 1 through 2, as a preliminary work to use 5-haloindoles 2 for a synthetic intermediate of 4-substituted indoles.



When 4-oxo-1-*p*-toluenesulfonyl-4,5,6,7-tetrahydroindole (1a) was heated with two equivalents of copper(II) bromide in ethyl acetate for 1 h, 5-bromo-4-oxo-1-*p*-toluenesulfonyl-4,5,6,7-tetrahydroindole (2a-Br) was produced in a 98% yield. The other *N*-substituted indoles 1b - 1d were similarly brominated with copper (II) bromide as shown in Table I. Free indole 1e (R = H) gave scarcely desired bromide 2e-Br by the use of $CuBr_2$. As a solvent, acetic acid, chloroform, dimethylformamide (DMF), and so on were usable in place of ethyl acetate, though the efficiency of the bromination decreased. Usage of excess $CuBr_2$ tended to form 5,5-dibromoindoles 3; treatment of 1a with 4 equivalents of $CuBr_2$ in ethyl acetate gave exclusively 5,5-dibromoindole 3a-Br. Another reagent, phenyltrimethylammonium perbromide ($PhNMe_3.Br_3$) was less effective than $CuBr_2$ for the bromination of 1 to 2.[5] Analogous reagent, pyridinium perbromide ($C_5H_5N.HBr_3$), gave somewhat improved result (yield of 2a-Br: 76%).

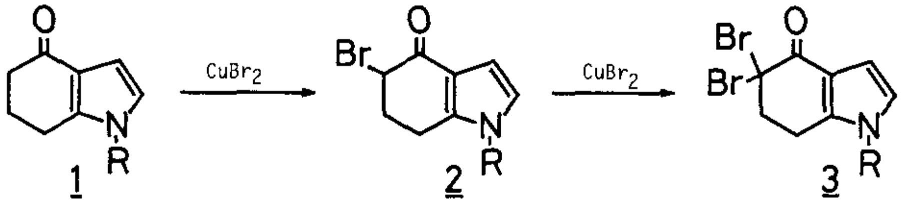


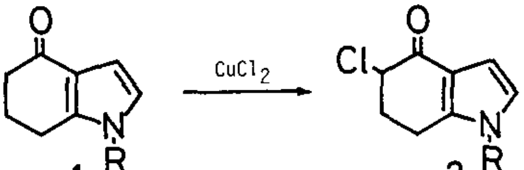
Table I. Bromination of 4-oxo-4,5,6,7-tetrahydroindoles (1) to 5-bromo-4-oxo-4,5,6,7-tetrahydroindoles (2) with copper(II) bromide.*

| Indole (1) R | | Solvent | Time (h) | Indole (2) | Mp (°C) | Yield (%)** |
|---|---|---|---|---|---|---|
| *p*-Toluenesulfonyl | (1a) | Ethyl acetate | 1 | (2a-Br) | 154-5 | 98 (98) |
| | | Chloroform | 4 | | | 82 (90) |
| | | Acetic acid | 4 | | | 67 (74) |
| | | 50% aq. AcOH | 4 | | | 83 (95) |
| | | DMF | 3 | | | 43 (88) |
| Benzenesulfonyl | (1b) | Ethyl acetate | 1 | (2b-Br) | 101-2 | 97 (97) |
| Methanesulfonyl | (1c) | Ethyl acetate | 3 | (2c-Br) | 113.5 | 89 (89) |
| Benzoyl | (1d) | Ethyl acetate | 2 | (2d-Br) | 130-1 | 74 (90) |

* All the reactions were carried out by the use of two equivalents of $CuBr_2$ at refluxing temperature.

** Figures in parenthesis mean selectivity of bromides 2.

Chlorination of indoles 1a and 1b to corresponding 5-chloroindoles 2 was achieved by the use of copper(II) chloride. As shown in table II, 50% aqueous acetic acid was far more favorable than acetic acid, chloroform, or ethyl acetate as the solvent used for the chlorination. Copper(II) chloride also converted N-benzylindole 1f and free indole 1e to the corresponding 5-chloroindoles 2f-Cl and 2e-Cl in moderate yields. These results were different from the case with copper(II) bromide (vide supra). Iron(III) chloride was of no use for the present purpose, though it is known as one of typical chlorinating reagents of ketones.[6] Sulfuryl chloride is also a convenient reagent for α-chlorination of ketones.[7] It was, however, not fit for use, because it mainly led to 2-chloro-4-oxo-tetrahydroindoles 4 instead of 5-chloroindoles 2 (see Experimental).



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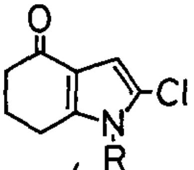

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Table II. Chlorination of 4-oxo-4,5,6,7-tetrahydroindoles (1) to 5-chloro-4-oxo-4,5,6,7-tetrahydroindoles (2) with copper(II) chloride.*

| Indoles (1) R | | Solvent | Time (h) | Indole (2) | Mp (°C) | Yield (%)** | |
|---|---|---|---|---|---|---|---|
| p-Toluenesulfonyl | (1a) | 50% aq. AcOH | 4 | (2a-Cl) | 152-3 | 86 | (86) |
| | | AcOH | 7 | | | 32 | (48) |
| | | Ethyl acetate<br>(Chloroform) | 5 | | | 2 | (68) |
| Benzenesulfonyl | (1b) | 50% aq. AcOH | 7 | (2b-Cl) | 139.5 | 92 | (92) |
| H | (1e) | 50% aq. AcOH | 4 | (2e-Cl) | 168(dec) | 46 | (69) |
| Benzyl | (1f) | 50% aq. AcOH | 12 | (2f-Cl) | 90.5-1.0 | 79 | (81) |

* All the reactions were carried out by the use of 2.2 equivalents of $CuCl_2$ at refluxing temperature.

** Figures in parenthesis mean selectivity of 2.

Stoichiometry of the present halogenation is shown as an equation:

$$\underline{1} \quad + \quad 2\ CuX_2 \quad \longrightarrow \quad \underline{2} \quad + \quad 2\ CuX \quad + \quad HX$$

Thus, considering that copper(I) halide is easily oxidized to copper(II) halide with dioxygen ($O_2$) in the presence of HX, one might think of a catalytic reaction: $\underline{1} \quad + \quad HX \quad + \quad 1/2\ O_2 \xrightarrow{"Cu"} \underline{2} \quad + \quad H_2O$

This idea was proved as follows: when indole 1a (1.0 g) was heated with copper (II) bromide (0.1 g) under an oxygen atmosphere in 50% aq. acetic acid (10 mL) containing HBr (0.33 g) for 7 h, 5-bromoindole 2a-Br was produced in a 72% yield (selectivity: 90%).

The results described here show that 5-halo-4-oxo-4,5,6,7-tetrahydroindoles (2) are now easily accessible.[8] Next, we examined dehydrohalogenation of 2 to 4-hydroxyindoles (5) as a preliminary work to use 2 for the synthesis of 4-substituted indoles. The aromatization of 2 was attained by the use of lithium salt/lithium carbonate in DMF as shown in Table III. This route (1→2→5) is useful for the preparation of N-protected 4-hydroxyindoles, which was, of course, able to be deprotected. Typical procedures to prepare 5-bromoindoles 2-Br, 5,5-dibromoindoles 3-Br, 5-chloroindoles 2-Cl, 2-chloroindoles 4, and 4-hydroxyindoles 5 are described in the following experimental section.

Table III. Synthesis of 4-hydroxyindoles (5) from 5-halo-4-oxo-4,5,6,7-tetrahydroindoles (2).

| Haloindole (2) | X | R | Time (h) | Hydroxyindole (5) | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| (2a-Br) | Br | p-Toluenesulfonyl | 1 | (5a) | 143.5-144.5 | 94 |
| (2a-Br)** | | | 2 | | | 98 |
| (2a-Cl) | Cl | p-Toluenesulfonyl | 3 | (5a) | | 98 |
| (2b-Br) | Br | Benzenesulfonyl | 1 | (5b) | 130.0-130.7 | 94 |
| (2c-Br) | Br | Methanesulfonyl | 1.5 | (5c) | 109.0-110.0 | 93 |
| (2d-Br) | Br | Benzoyl | 1 | (5d) | 149.0-150.0 | 98 |

* Unless otherwise stated, the dehydrohalogenation was carried out under the following conditions; 2:LiBr:$LiCO_3$ = 1:1.05:1.05, DMF, $N_2$ or Ar atmosphere, 150°C. **In place of LiBr, LiCl was used.

EXPERIMENTAL

5-Bromo-4-oxo-N-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2a-Br) Copper(II) bromide(1.55g, 6.92 mmol) was stirred together with 4-oxo-N-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (1a) (1.00 g, 3.46 mmol) in ethyl acetate (10 mL) under an argon atmosphere at refluxing temperature for 45 min. From the hot solution, copper(I) bromide was filtered off. The mother liquid was diluted with $CH_2Cl_2$, washed with $H_2O$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel. Elution with $CH_2Cl_2$-hexane (1:1) gave the 5-bromoindole 2a-Br in a 98% yield (1.25 g). Colorless prisms melted at 154 - 155°C (from ethyl acetate). NMR($CDCl_3$) 2.32-2.54 (m, 2H), 2.42 (s, 3H), 3.00-3.18 (m, 2H), 4.46 (t, J=4.2Hz, 1H), 6.61 (d, J=3.9Hz, 1H), 7.20-7.84 (m, 5H)ppm. IR(KBr) 1680, 1600, 1393, 1180, 1122 $cm^{-1}$. Mass(m/z,%) 369 ($M^+$, 29), 367 ($M^+$, 29), 155 (47), 106 (90), 91 (100).

5,5-Dibromo-4-oxo-N-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (3a-Br) A solution of 4-oxo-N-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (1a) (1.00 g, 3.46 mmol) and copper(II) bromide (3.20 g, 14.3 mmol) in ethyl acetate (15 mL) was refluxed for 6 h. The solution was diluted with $CH_2Cl_2$ (80 mL) and filtered to remove copper(I) bromide. The mother liquid was washed with $H_2O$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel. Elution with $CH_2Cl_2$ gave the dibromoindole 3a-Br in a 99% yield (1.53 g). Colorless prisms melted at 152.0 - 153.2°C (from ethyl acetate). NMR($CDCl_3$) 2.43 (s, 3H), 2.92-3.18 (m, 4H), 6.65 (d, J=3.9Hz, 1H), 7.20-7.80 (m, 5H) ppm. IR(KBr) 1690, 1595, 1375, 1187, 1175 $cm^{-1}$. Mass (m/z,%) 449 ($M^+$, 1.8), 447 ($M^+$, 3.3), 445 ($M^+$, 1.7), 155 (34), 106 (84), 91 (100).

5-Chloro-4-oxo-N-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2a-Cl) A solution of 4-oxo-1-p-toluenesulfonyl-4,5,6,7-tetrahydroindole (1a) (1.00 g, 3.46 mmol) and copper(II) chloride (1.02 g, 7.61 mmol) in 50% aq. acetic acid (10 mL) was refluxed under an argon atmosphere for 3.5 h. After removal of copper(I) chloride, the solution was poured into $H_2O$ and extracted with $CH_2Cl_2$. The organic layer was washed with $NaHCO_3$ aq. solution, dried over $MgSO_4$, and then concentrated. Chromatographic purification of the residue [$SiO_2/CH_2Cl_2$-hexane (1:1)] afforded the 5-chloroindole 2a-Cl in an 86% yield (0.96 g). Colorless prisms melted at 152 - 153°C (from ethyl acetate). NMR($CDCl_3$) 2.36-2.58 (m, 2H), 2.46 (s, 3H), 3.16-3.24 (m, 2H), 4.44 (t, J=4.0 Hz, 1H), 6.68 (d, J=3.2Hz, 1H), 7.28-7.48 (m, 3H), 7.74-7.87 (m, 2H)ppm. IR(KBr) 1680, 1600, 1387, 1178 $cm^{-1}$. Mass(m/z,%) 323 ($M^+$, 26), 106 (100), 91 (66).

2-Chloro-4-oxo-N-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (4a) To a solution of 4-oxo-N-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (1a) (1.00 g, 3.46 mmol) in $CH_2Cl_2$ (10 mL), a solution of surfuryl chloride (0.52 g, 3.85 mmol) in $CH_2Cl_2$ (5 mL) was added at 0°C and stirred for 1 h at room temperature. The solution was stirred with $K_2CO_3$ (2.0 g) for 30 min and was concentrated. The residue was chromatographed on silica gel. Elution with $CH_2Cl_2$ afforded the 2-chloroindole 4a in a 56% yield. Colorless granules melted at 189.0 - 190.0°C (from $CH_2Cl_2$). NMR($CDCl_3$) 1.90-2.46 (m, 4H), 2.32 (s, 3H), 3.10 (m, 2H), 6.35 (s, 1H), 7.16-7.80 (m, 4H) ppm. IR(KBr) 1678, 1600, 1388 $cm^{-1}$. Mass(m/z,%) 323 ($M^+$, 16), 155 (61), 91 (100).

4-Hydroxy-N-(p-toluenesulfonyl)indole (5a) A solution of 5-bromo-4-oxo-N-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2a-Br) (200 mg, 0.543 mmol) in DMF (10 mL) was heated together with LiBr (50 mg, 0.576 mmol) and $Li_2CO_3$ (79 mg, 0.572 mmol) under a nitrogen atmosphere at 150°C for 1 h. The reaction mixture was poured into aq. $NH_4Cl$ solution and was extracted with $CH_2Cl_2$. The organic layer was washed twice with $H_2O$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel and eluted with $CH_2Cl_2$-ethyl acetate (100:1) to give the 4-hydroxyindole 5a in a 94% yield (145 mg). Colorless prisms melted at 143.5-144.5°C (from ethyl acetate-hexane). NMR($CDCl_3$) 2.31 (s, 3H), 5.25 (broad s, 1H), 6.48-7.84 (m, 9H) ppm. IR(KBr) 3480, 1600, 1500, 1365, 1127 $cm^{-1}$. Mass(m/z,%) 287 ($M^+$, 33), 132 (100), 91 (27).

## REFERENCES AND NOTES

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   b) W. A. Remers and M. J. Weiss, ibid., 1971, **36**, 1241.
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6. Y. Nakatani, K. Kakinuma, and M. Matsui, Tetra. Letters, 1967, 4085.
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8. The starting material, 4-oxo-4,5,6,7-tetrahydroindole (1e), can be easily prepared from 1,3-cyclohexanedione and chloroacetaldehyde.[9] N-Protected ones (1a - 1f) are also selectively synthesized by condensation of an anion of 1e and the corresponding halides.
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