A FACILE ONE STEP SYNTHESIS OF 4-AMINOINDOLES FROM 5-HALO-4-OXO-4,5,6,7-TETRAHYDROINDOLES

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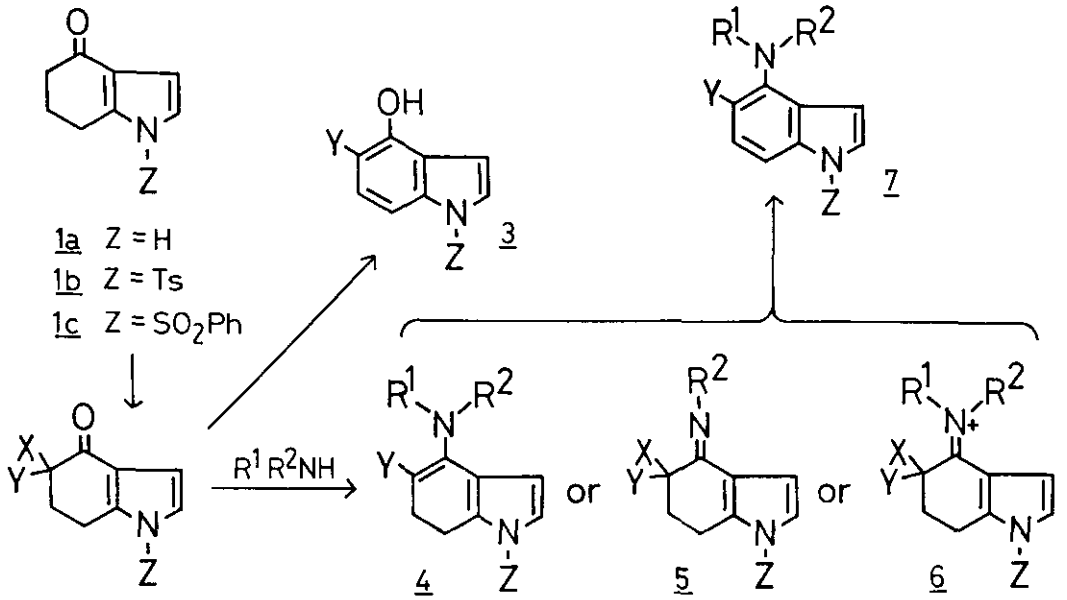
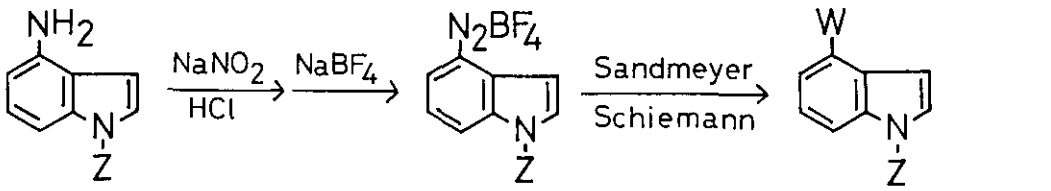
Abstract ——— Reaction of 5-halo-4-oxo-4,5,6,7-tetrahydroiondoles with amines initiates the amination of the carbonyl function and ensuing dehydrohalogenation leads to a successful formation of 4-aminoindoles.

Indoles bearing functionalities at 4-position have been drawing considerable attention owing to their wide variety of biological activities.[1] Among them, 4-aminoindole derivatives should be of great importance, because some biologically active compounds carries nitrogen function at 4-position[2] and also amino group can be converted into other functionalities such as hydroxy-, halo- and cyano-groups through diazotization.[3] In spite of such obvious importance of 4-aminoindoles, no definitive method of their preparation has yet been devised. All the reported methods for 4-aminoindole derivatives start either from 2-halo-6-nitrotoluene or from 2,6-dinitrotoluene.[3,4] These reported methods require lengthy procedure, drastic condition, and sometimes expensive reagent.

Our approach to the 4-aminoindole derivatives is totally different from the conventional 4-substituted indole synthesis.[1] We planned to utilize the 4-oxo-4,5,6,7-tetrahydroindole (1a) as a starting compound. Although 1a carries a seemingly convenient handle (carbonyl group) at the 4-position, only a few attempts have been made so far to convert 1a into 4-substituted indoles.[5] Since we have developed a convenient procedure for the synthesis of 1a,[6] construction of the 4-substituted indoles from 1a has become much more attractive and practical alternative to the older methods. When 1 is converted into indole ring system, it requires dehydrogenative oxidation. We have already solved this problem by oxidizing 1b or 1c into 5-halotetrahydroindole, 2a, 2b or 2c by the use of copper(II) halide.[7] Transformation of the carbonyl group and subsequent





7a Z = Ts
7b Z = SO_2Ph

8a Z = Ts
8b Z = SO_2Ph

9a Z=Ts, W=Cl
9b Z=Ts, W=Br
9c Z=Ts, W= I
9d Z=Ts, W= F
9e Z=SO_2Ph, W=F

dehydrohalogenation will directly provide a convenient method for the synthesis of 4-substitued indoles. We report here the one step synthesis of 4-aminoindole derivatives by the reaction of amines with 5-halo-4-oxo-4,5,6,7-tetrahydroindoles 2.

In order to make this approach feasible, careful adjustment of reaction condition was required. Namely, formation of enamine 4, imine 5 or iminium salt 6 has to precede the dehydrohalogenation. If this order is reversed, one only gets 4-hydroxyindole derivatives 3 as a result of dehydrohalogenation without incorporation of amino function. When 5-chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2a) was heated with amines in toluene in a sealed tube, amination at the 4-position and dehydrochlorination took place simultaneously to give 4-amionoindole derivatives 7 (entries 5 and 8). To avoid the hazard of heating highly volatile amines in a sealed tube and to promote the enamine formation, addition of acetic acid to the system was attempted and was successful (entries 1, 2, 3, 4 and 6).[8] Acetic acid made the amines into less volatile acetate salt and simple refluxing in xylene in an open system was sufficient for the intended transformation. The results are summarized in Table I.

Table I. 4-Aminoindoles 7 from 5-halo-4-oxo-4,5,6,7-tetrahydroindoles 2

Entry	2	Amines	Solvent	Time(h)	Conv.(%)	Yield 7(%)
1	2a	$NH_3(AcONH_4)$	Xylene(AcOH)	4	93	7a 72
2	2b	$NH_3(AcONH_4)$	Xylene(AcOH)	15	76	7i 73
3	2c	$NH_3(AcONH_4)$	Xylene(AcOH)	2.5	100	7b 92
4	2a	$MeNH_2$	Xylene(AcOH)	2	100	7c 78
5[a)]	2a	n-$C_4H_9NH_2$	Tolune	24	100	7d 64
6	2a	Allylamine	Xylene(AcOH)	3	100	7e 46
7	2a	$PhCH_2NH_2$	Toluene	24	100	7e 46
8[a)]	2a	Morpholine	Toluene	24	100	7g 22
9[b)]	2a	$PhNH_2$	Toluene	1	100	7h 96

a) In a sealed tube.

b) Catalytic amount of p-toluenesulfonic acid was used.

Free amino derivatives 7a, 7b were further transformed into diazonium tetrafluoroborates 8a (91 %) and 8b (93 %) by the standard diazotization procedure.[3] These diazonium salts 8a, 8b are surprisingly stable at room temperature and decompose without explosive force when heated above 100 °C. Compounds 8a and 8b are transformed into 4-halo-substituted indoles 9 either by Sandmeyer reaction or by Schiemann reaction.[9] The results are summerized in Table II.

Table II. 4-Haloindoles 9 from 4-aminoindoles 7

Entry	8	Reagent	9	Yield(%)	mp (°C)
1	8a	HCl-CuCl	9a(Cl)	71	119 - 120
2	8a	HBr-CuBr	9b(Br)	91	119 - 120
3	8a	KI	9c(I)	74	92 - 93
4	8a	none	9d(F)	52	85 - 87
5	8b	none	9e(F)	62	110 - 112

Now that we have demonstrated the usefulness of 4-oxo-4,5,6,7-tetrahydroindole 1 by transforming it into 4-aminoindoles, the search of other use of this versatile starting material is actively underway.

EXPERIMENTAL

4-Amino-1-(p-toluenesulfonyl)indole (7a). A mixture of 5-chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2a) (3.66 g, 11.3 mmol), ammonium acetate (8.71 g, 113.0 mmol) and acetic acid (0.4 ml) in p-xylene (20 ml) was heated to reflux for 4 h. After the mixture was cooled, it was poured onto saturated aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 . The CH_2Cl_2 solution was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel. Elution with CH_2Cl_2 gave 4-amino-1-(p-toluenesulfonyl)indole (7a) (2.32 g, 71.8 %). Colorless needles melted at 130 - 131 °C (from ether). NMR ($CDCl_3$) δ 2.30(s, 3H), 3.68 (s, broad, 2H), 6.44 (d, J=8.0 Hz, 1H), 6.52 (d, J=4.0 Hz, 1H), 6.96 - 7.48 (m, 5H) and 7.71 (d, J=8.0 Hz, 2H) ppm. IR (KBr) 3500, 3400, 1630, 1600, 1360 and 1165 cm^{-1}. Mass (m/z, %) 286 (M^+, 34) and 132 (100).

4-Amino-1-(bezenesulfonyl)indole (7b). A mixture of 1-benezenesulfonyl-5-

chloro-4-oxo-4,5,6,7-tetrahydroindole (2c) (75 mg, 0.24 mmol), ammonium acetate (185 mg, 2.40 mmol) and acetic acid (0.1 ml) in p-xylene (5 ml) was heated to reflux for 2.5 h. Usual work-up and chromatography (CH_2Cl_2) gave 4-amino-1-(benzenesulfonyl)indole (7b) (60 mg, 92.0 %). Colorless needles melted at 117-118 °C (from ether). NMR ($CDCl_3$) δ 3.73 (s, broad, 2H), 6.27 - 6.54 (m, 2H), 6.82 - 7.48 (m, 6H) and 7.63 - 7.97 (m, 2H) ppm. IR (KBr) 3480, 3400, 1635, 1600, 1370, 1190 and 1130 cm^{-1}. Mass (m/z, %) 272 (M^+, 29) and 131 (100).

4-Amino-5-chloro-1-(p-toluenesulfonyl)indole (7i). A mixture of 5,5-dichloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2b) (1.04 g, 2.91 mmol), ammonium acetate (2.25 g, 29.1 mmol) and acetic acid (0.2 ml) in p-xylene (10 ml) was heated to reflux for 15 h. Usual work-up and chromatography (CH_2Cl_2) gave 4-amino-5-chloro-1-(p-toluenesulfonyl)indole (7i) (682 mg, 73.0 %). Colorless needles melted at 138 - 139 °C (from ether). NMR ($CDCl_3$) δ 2.14 (s, 2H), 2.32 (s, 3H), 7.06 - 7.54 (m, 6H) and 7.69 (d, J=8.0 Hz, 2H) ppm. IR(KBr) 3470, 3400, 1625, 1600, 1360 and 1170 cm^{-1}. Mass (m/z, %) 321 (M^+, 59), 323 (M+2, 23), 168 (33), 167 (35), 166 (100), 165 (76), 155 (31) and 91 (80).

4-(N-Methylamino)-1-(p-toluenesulfonyl)indole (7c). 5-Chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2a) (713 mg, 2.20 mmol) was dissolved in a mixture of p-xylene (10 ml) and acetic acid (0.2 ml). After methylamine (683 mg, 22.0 mmol) and acetic acid (1.32 g, 22.0 mmol) was added to the solution, the mixture was heated to reflux for 2 h. Usual work-up and chromatography (CH_2Cl_2) gave 4-(N-methylamino)-1-(p-toluenesulfonyl)indole (7c) (516 mg, 78.2 %). Colorless needles melted at 139 - 140 °C (from ether). NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.88 (s, 3H), 6.37 (d, J=7.9 Hz, 1H), 6.54 (d, J=4.0 Hz, 1H), 7.08 - 7.48 (m, 6H) and 7.76 (d, J=8.0 Hz, 2H) ppm. IR (KBr) 3450, 2830, 1600, 1360 and 1165 cm^{-1}. Mass (m/z, %) 300 (M^+, 40), 145 (100) and 117 (67).

4-(N-Allylamino)-1-(p-toluenesulfonyl)indole (7e). 5-Chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2a) (625 mg, 1.93 ml) was dissolved in a mixture of p-xylene (10 ml) and acetic acid (0.2 ml). After allyamine (1.10 g, 19.3 mmol) was added to the solution, the mixture was heated to reflux for 3 h. Usual work-up and chromatography gave 4-(N-allylamino)-1-(p-toluenesulfonyl)indole (7e) (290 mg, 46.1 %) as an oil. NMR ($CDCl_3$) δ 2.23 (s, 3H), 3.70 - 3.86 (m, 2H), 3.98 (s, broad, 1H), 5.02 - 5.35 (m, 2H), 5.74 - 6.12 (m, 1H), 6.32 (d, J=8.0 Hz, 1H), 6.50 (d, J=3.8 Hz, 1H), 7.00 - 7.45 (m, 5H) and

7.67 (d, J= 8.0 Hz, 2H) ppm. IR (KBr) 3450, 1600, 1515, 1370 and 1170 cm^{-1}. Mass (m/z, %) 326 (M^+, 42), 171 (100) and 156 (30).

4-(N-Butylamino)-1-(p-toluenesulfonyl)indole (7d). A mixture of 5-chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (2a) (545 mg, 1.68 mmol) and n-butylamine (368 mg, 5.04 mmol) in toluene (2 ml) was heated at 140 °C for 24 h in a sealed tube. The mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 gave 4-(N-butylamino)- 1-(p-toluenesulfonyl)indole (7d) (371 mg, 64.4 %). Colorless needles melted at 103 - 104 °C (from ether). NMR ($CDCl_3$) δ 0.85 - 1.05 (m, 3H), 1.23 - 1.79 (m, 4H), 2.29 (s, 3H), 3.26 - 3.68 (m, 2H), 3.78 (s, broad, 1H), 6.33 (d, J=8.0 Hz, 1H), 6.50 (d, J=3.7 Hz, 1H), 7.02 - 7.45 (m, 5H) and 7.70 (d, J=8.0 Hz, 2H) ppm. IR (KBr) 3450, 1610, 1600, 1510, 1370 and 1170 cm^{-1}. Mass (m/z, %) 342 (M^+, 4) and 187 (100).

4-(N-Phenylamino)-1-(p-toluenesulfonyl)indole (7h). A mixture of 5-chloro-4-oxo-1-(p-toluenesulfonyl)indole (2a) (520 mg, 1.61 mmol), aniline (450 mg, 4.83 mmol) and p-toluenesulfonic acid (50 mg. 0.26 mmol) in toluene (10 ml) was heated to reflux for 1 h under an argon atomosphere. Concentration and chromatography (CH_2Cl_2) gave N-phenylamino-1-(p-toluenesulfonyl)indole (7h) (560 mg, 96.1 %). Colorless needles melted at 166 - 167 °C. NMR ($CDCl_3$) δ 2.33 (s, 3H), 6.54 (d, J=4.0 Hz, 1H), 6.80 - 7.32 (m, 10H), 7.44 - 7.62 (m, 2H) and 7.74 (d, J=8.0 Hz, 2H) ppm. IR (KBr) 3450, 1600, 1510, 1370 and 1170 cm^{-1}. Mass (m/z, %) 362 (M^+, 48), 207 (100) and 106 (67). Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73; S, 8.85. Found: C, 69.23; H, 4.96; N, 7.70; S, 9.03.

1-(p-Toluenesulfonyl)-4-indolediazonium Tetrafluoroborate (8a). To a suspension of 4-amino-1-(p-toluenesulfonyl)indole (7a) (270 mg, 0.84 mmol) in a mixture of H_2O (6.5 ml) and 2N HCl (1.6 ml) was added dropwise $NaNO_2$ (141 mg, 2.04 mmol) in H_2O (3 ml) at 0 °C. After the mixture was stirred for 20 min at 0 °C, saturated aq. $NaBF_4$ solution (1.6 ml) was added. The mixture was stirred at 0 °C for 20 min and at room temperature for 30 min. Precipitates were collected by suction filtration, washed with a small amount of H_2O and then with CH_2Cl_2. The precipitates were dried over P_2O_5 in vacuo to give 281 mg (90.5 %) of 1-(p-toluenesulfonyl)-4-indolediazonium tetrafluoroborate (8a). Pale yellow needles (from methanol) decomposed at 130 - 132 °C. NMR (DMSO-d_6) δ 2.36 (s, 3H), 7.50

(d, J=8.2 Hz, 2H), 7.56 (d, J=3.8 Hz, 1H), 7.90 (t, J=8.0 Hz, 1H), 8.08 (d, J=8.2 Hz, 2H), 8.60 (d, J=3.8 Hz, 1H), 8.74 (d, J=8.0 Hz, 1H) and 8.88 (d, J=8.0 Hz, 1H) ppm. IR (KBr) 2260, 1370, 1170, 1085 and 680 cm^{-1}. Mass (m/z, %) 289 ($M^+ - N_2.BF_3$, 71), 155 (100), 91 (95) and 28 (68). Anal. Calcd for $C_{15}H_{12}BF_4N_3O_2S$: C, 46.78; H, 3.14; N, 10.91. Found: C, 46.65; H, 3.02; N, 10.78.

4-Bromo-1-(p-toluenesulfonyl)indole (9b). To a suspension of Cu_2Br_2 (795 mg, 5.5 mmol) in a mixture of H_2O (2 ml) and conc. HBr (2 ml) was added dropwise 1-(p-toluenesulfonyl)-4-indolediazonium tetrafluoroborate (8a) (70 mg, 0.18 mmol) in acetone (2 ml) at 0 °C under an argon atomosphere. The mixture was stirred at room temperature for 3 h and at 94 °C for 15 min. Usual work-up and chromatography (CH_2Cl_2-hexane) gave 4-bromo-1-(p-toluenesulfonyul)indole (9b) (57 mg, 91 %) as a colorless solid. Sublimed 9b metled at 119 - 120 °C. NMR ($CDCl_3$) δ 2.33 (s, 3H), 6.67 (d, J=4.0 Hz, 1H), 6.97 - 7.47 (m, 4H) and 7.50 - 8.00 (m, 4H) ppm. IR (KBr) 1375, 1170, 760, 680 and 580 cm^{-1}. Mass (m/z, %) 351 (M^+, 36), 349 (M^+, 34), 155 (68) and 91 (100). Anal. Calcd for $C_{15}H_{12}BrNO_2S$: C, 51.44; H, 3.45; N, 4.00. Found: C, 51.62; H, 3.27; N, 3.85.

4-Iodo-1-(p-toluenesulfonyl)indole (9c). To a solution of KI (1.13 g, 6.8 mmol) in acetone (2 ml) was added 1-(p-toluenesulfonyl)-4-indolediazonium tetrafluoroborate (8a) (50 mg, 0.13 mmol) at 0 °C. After the mixture was stirred at 0 °C for 10 min and at room temperature for 1 h, it was poured onto saturated aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, concentrated and chromatographed on silica gel. Elution with CH_2Cl_2-hexane gave 4-iodo-1-(p-toluenesulfonyl)indole (9c) (38 mg, 74 %) as a colorless solid. Sublimed 9c melted at 92 - 93 °C. NMR ($CDCl_3$) δ 2.33 (s, 3H), 6.57 (d, J=4.0 Hz, 1H), 6.77 - 7.30 (m, 3H) and 7.37 - 7.97 (m, 5H) ppm. IR (KBr) 1375, 1170, 685 and 580 cm^{-1}. Mass (m/z, %) 397 (M^+, 31), 271 (47), 155 (61), 116 (33) and 91 (100). Anal. Calcd for $C_{15}H_{12}INO_2S$: C, 45.35; H, 3.05; N, 3.53. Found: C, 45.51; H, 3.09; N, 3.49.

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