SYNTHESIS OF 4-CYANOINDOLE FROM 4-OXO-4,5,6,7-TETRAHYDROINDOLE DERIVATIVES

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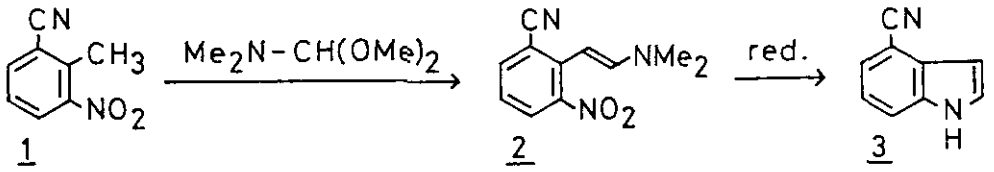
Abstract —— *4-Oxo-4,5,6,7-tetrahydroindoles are first converted to* cyanohydrin silyl ethers and subsequent elimination and/or oxidation produced 4-cyanoindole.

4-Substituted indoles with C_1-unit functionality such as cyano or formyl group should be very useful key compounds in terms of versatility and reactivity of the function. Cyano group seems to be especially attractive because it can be converted into amine, aldehyde or alcohol by reduction, carboxylic acid by hydrolysis, and ketone by reaction with alkyl metal species. With all these prospects of 4-cyanoindole, only a few reports on utilization of this derivative have appeared in the literature. *Troxler converted 4-cyanoindole into* 4-formylindole for further transformation,[1] Oppolzer and Grayson suggested 4-cyanoindole as a starting key compound for their ergot alkaloid synthesis,[2] and *Clark converted* 4-cyanoindole into a methyl ketone derivative to synthesize 4-(2-morpholino)indoles.[3] One of the reasons for such scarce use of 4-cyanoindole was the lack of effective method for its synthesis. All the reported methods[3,4,5] are either lengthy, expensive or unpractical. The most commonly employed method for the 4-substituted indoles was Leimgruber-Batcho approach,[6,7] which has also been applied to 4-cyanoindole synthesis.[3]



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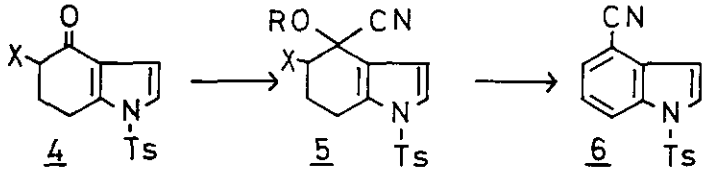
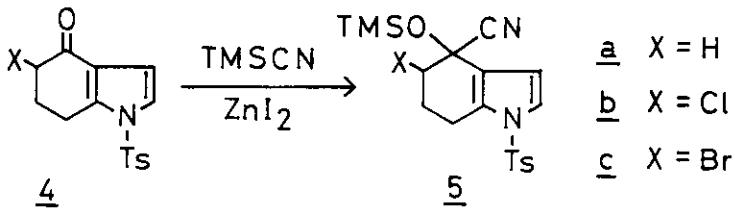
However, the method requires cyano-substituted o-nitrotoluene which is not easy to come by, the reagent DMFDMA(N,N-dimethylformamide dimethylacetal) is

expensive and reduction step is quite tricky to control.

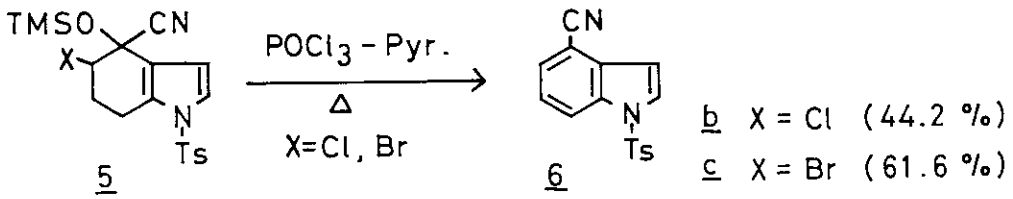
Our approach toward 4-substituted indoles is totally different from conventional methods and involves the use of 4-oxo-4,5,6,7-tetrahydroindole derivative as a key intermediate. Since we have reported a convenient procedure for the preparation of 4-oxo-4,5,6,7-tetrahydroindole[8] and its preliminary transformation toward 4-substituted indoles,[9] we are now in a position to find a good use of this versatile intermediate. In fact we have already established a facile method for the syntheis of 4-amino and 4-halo-substituted indoles from this key compound.[10] Most reasonable and obvious approach from 4-oxotetrahydroindole derivative such as 4 to cyanoindole 6 seems to be cyanohydrin formation and subsequent aromatization leaving the cyano group intact. However ordinary method for cyanohydrin formation with hydrogen cyanide can not be applied here because it is a conjugated ketone. Only solution to this problem is the use of cyanotrimethylsilane with zinc iodide catalyst to form cyanohydrin silyl ether species 5. It has been reported that this method is successful with similar system like tetralone.[11]



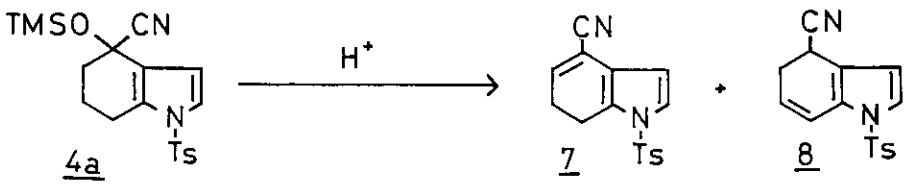
Accordingly 4-oxotetrahydroindoles (4a, 4b and 4c) are mixed with excess cyanotrimethylsilane (usually 2 molar equivalents) and catalytic amount of zinc iodide and the mixture was stirred at ambient temperature for 2 - 18 h to produce the corresponding cyanohydrin silyl ethers (5a, 5b and 5c) in quantitative yields. Although a simple work-up procedure described in the experimental section provided sufficiently pure samples for further reactions, these cyanohydrin silyl ethers also stand a quick silica gel column purification with some loss of the materials in the process. 5-Halo-substituted derivatives (5b and 5c) seem to be more stable under chromatographic condition than 5a and resists destruction of the silyl ether part probably because 5-substituent (halogen) shields the labile cyanohydrin silyl ether from hydrolysis. 5-Bromo-derivative 5c in a pure solid state, however, quickly deteriorates upon standing at ambient temperature.



5-Halo-substituted cyanohydrin silyl ether (5b and 5c) under typical condition (heating with phosphorus oxychloride in pyridine) simultaneously eliminated hydrogen halide along with silanol unit to give the desired 1-(p-toluenesulfonyl)-4-cyanoindole 6 with modest yields.



Halogen-absent cyanohydrin silyl ether 4a under acidic condition (p-toluenesulfonic acid in refluxing benzene or toluene) produced a mixture of dihydroindole derivatives 7 and 8.

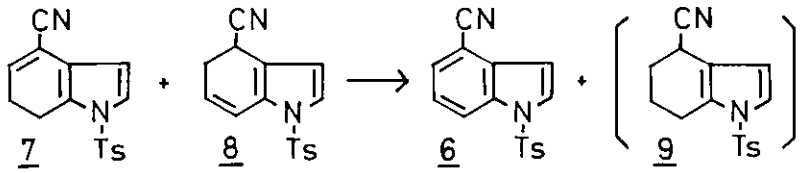


Catalyst	Solvent	Condition	Yield(%)	7 : 8
TsOH	PhH	reflux(2h)	64.7	2:1
TsOH	$PhCH_3$	reflux(2h)	83.9	3:1

Dehydrogenative oxidation has to be conducted on the dihydroindole derivatives (7 and 8) to produce the final target compound 4-cyanoindole 6. Firstly catalytic dehydrogenation was attempted under various conditions as shown in Table I. The formation of hydrogen transfer product such as tetrahydroindole 9 is always the problem when catalytic dehydrogenation is employed for this type of transformation. After optimal condition to suppress the formation of 9 was surveyed at the fixed reaction time (2h), it turned out that palladium catalyzed reaction with relatively low boiling mixed solvent system (AcOH - H_2O 1:1)

showed the excellent selectivity eliminating the formation of 9 completely. Other metals like platinum, ruthenium or rhodium are totally ineffective for this type of dehydrogenation.

Table I Catalytic Dehydrogenation

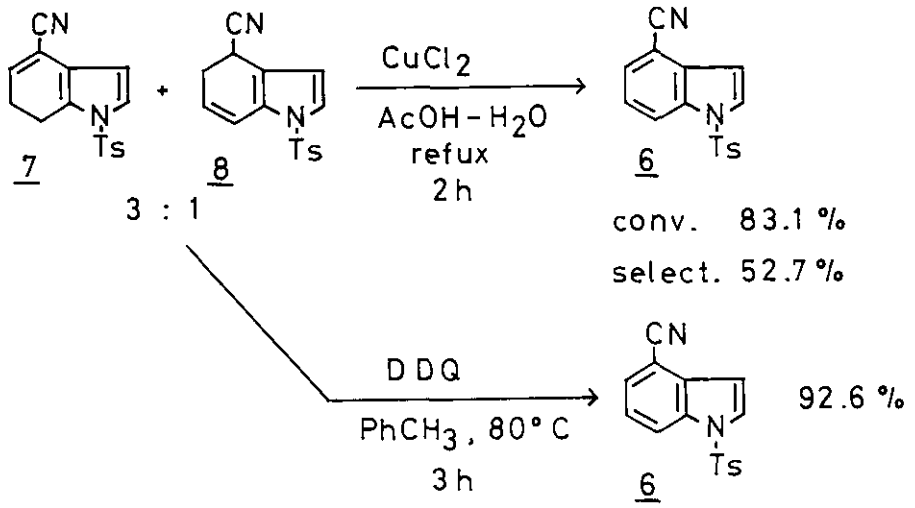


3 : 1

Entry	Catalyst	Solvent (Temp.)	Time(h)	Conv.(%)	Select. 6(%)	9(%)
1	5% Pd-C	Cymene (180°)	2	78.3	76.8	18.2
2	5% Pd-C(S)[a)]	Cymene	2	93.8	66.6	7.6
3	5% Pd-C	$(EtOCH_2CH_2)_2O$ (185°)	2	75.3	51.0	9.4
4	5% Pd-C	AcOH-H_2O	2	72.8	97.4	0
5	5% Pd-C	MEK(100°)	2	83.6	67.3	22.5
6	5% Pd-C	AcOH(120°)	2	100	57.9	24.7
7	5% Pt-C	AcOH	2	NO REACTION		
8	5% Ru-C	AcOH	2	NO REACTION		
9	5% Rh-C	AcOH	2	NO REACTION		

a) Sulfur was added as a catalyst poison.

Other oxidizing agents were also tried for the 4-cyanoindole formation. The mixture of dihydroindoles (7 and 8) was heated with cupric chloride in aqueous acetic acid to produce some 4-cyanoindole 6 with low selectivity. The same dihydroindole mixture was treated with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to afford cyanoindole 6 in an excellent yield (92.6 %).



Now that we have developed a simple efficient way of preparing 4-cyanoindole from the readily available key-intermediate 4-oxo-4,5,6,7-tetrahydroindole, one will find 4-cyanoindole an attractive alternative to other existing intermediates for 4-substituted indole synthesis.

EXPERIMENTAL

4-Cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5a). A mixture of 4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (4a) (826 mg, 2.9 mmol), cyanotrimethylsilane (595 mg, 6.0 mmol) and ZnI_2 (96 mg, 0.3 mmol) was stirred at ambient temperature for 2 h. Ether (50 ml) was added to the mixture and the ethereal solution was washed with water, saturated aq. NaCl solution, and dried over $MgSO_4$. The drying agent was filtered off and the filtrate was concentrated to dryness to give 4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5a) (1.1g, 99.2 %). Mp 91.5 - 92.5 °C (purified by sublimation). NMR ($CDCl_3$) δ 0.12 (s, 9H), 1.74 - 2.21 (m, 4H), 2.42 (s, 3H), 2.58 - 2.83 (m, 2H), 6.40 (d, J=3.5 Hz, 1H), 7.17 - 7.42 (m, 3H) and 7.69 (d, J=8.4 Hz, 2H) ppm. IR (KBr) 2980, 1600, 1380, 1255, 1180, 1130, 850, 710 and 600 cm^{-1}. Mass (m/z, %) 388 (M^+, 48), 362 (31), 299 (30), 298 (30), 206 (29), 205 (43), 155 (37), 143 (45), 106 (29), 91 (100), 75 (38) and 73 (68). Anal. Calcd for $C_{19}H_{24}N_2O_3SSi$: C, 58.73; H, 6.23; N, 7.21; S, 8.25. Found: C, 58.68; H, 6.29, N, 7.18; S, 8.26.

5-Chloro-4-cyano-1-(p-toluenesufonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5b). A solution of 5-chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-

tetrahydrosulfonylindole (4b) (1.16 g, 3.6mmol), cyanotrimethylsilane (0.71 g, 7.2 mmol) and ZnI_2 in benzene (5 ml) was stirred at ambient temperature for 2 h. Dichloromethane (50 ml) was added and the solution was washed with saturated aq. $NaHCO_3$ solution, saturated aq. NaCl solution, and dried over $MgSO_4$. The drying agent was filtered off and the filtrate was concentrated. The residue was chromatographed on a silica gel column with dichloromethane to give 5-chloro-4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5b) (1.453 g, 95.9 %). Mp 112 - 113 °C (from toluene-pentane). NMR ($CDCl_3$) δ 0.12 (s, 9H), 2.03 - 2.57 (m, 3H), 2.42 (s, 3H), 2.64 - 3.20 (m, 2H), 4,20 (dd, J=5,2 Hz, J=4,5 Hz, 1H), 6.42 (d, J=3.3 Hz, 1H), 7.18 - 7.42 (m, 3H) and 7.71 (d, J=8.4 Hz, 2H) ppm. IR (KBr) 2970, 1600, 1380, 1255, 1180, 1140, 850, 705 and 675 cm^{-1}. Mass (m/z, %) 424 (M^+, 6), 422(M^+, 13), 360 (66), 205 (77), 155 (28), 106 (40), 91 (100) and 73 (61). Anal. Calcd for $C_{19\ 23}ClN_2O_3SSi$: C, 53.95; H, 5.48; N, 6.62; S, 7.58; Cl, 8.38. Found: C, 53.97; H, 5.43; N, 6.58; S, 7.57; Cl, 8.49.

5-Bromo-4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5c). A mixture of 5-bromo-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahyodroindole (4c) (368 mg, 1.0 mmol), cyanotrimethylsilane (200 mg, 2.0 mmol) and ZnI_2 (32mg, 0.1 mmol) was stirred at ambient temperature for 18 h. Dichloromethane (50 ml) was added and the solution was washed with saturated aq. $NaHCO_3$ solution, saturated aq. NaCl solution and dried over $MgSO_4$. The drying agent was filtered off and the filtrate was concentrated. The residue was chromatographed on a silica gel column with dichloromethane to give 5-bromo-4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5c) (444 mg, 95.0 %). NMR ($CDCl_3$) δ 0.12 (s, 9H), 2.22 - 2.67(m, 2H), 2.42 (s, 3H), 2.72 - 2.99 (m, 2H), 4,28 (dd, J=8.9 Hz, J=5,6 Hz, 1H), 6.42 (d, J=3.5 Hz, 1H), 7.22 - 7.45 (m, 3H) and 7.70 (d, J= 8.6 Hz, 2H) ppm. IR (KBr) 2970, 1600, 1380, 1255, 1180, 1130, 845 and 670 cm^{-1}. Mass (m/z, %) 468 (M+1, 14), 360 (78), 205 (78), 155 (35), 119 (67), 117 (69), 106 (35), 91 (100) and 73 (64).

4-Cyano-1-(p-toluenesulfonyl)-6,7-dihydroindole (7) and 4-Cyano-1-(p-toluenesulfonyl)-4,5-dihydroindole (8). A solution of 4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5a) (3.693 g, 9.5 mmol) and p-toluenesulfonic acid (50 mg, 0.3 mmol) in toluene (50 ml) was heated to reflux

for 4.5 h. The solvent was removed and the residue was chromatographed on a silica gel column with dichloromethane to give a mixture of 4-cyano-1-(p-toluenesulfonyl)-6,7-dihydroindole (7) and 4-cyano-1-(p-toluenesulfonyl)-4,5-dihydroindole (8) (2.344, 82.7 %).

4-Cyano-1-(p-toluenesulfonyl)-6,7-dihydroindole (7): Mp 108 - 109 °C (from toluene-hexane). NMR ($CDCl_3$) δ 2.32 - 2.69 (m, 2H), 2.41 (s, 3H), 2.83 - 3.12 (m, 2H), 6.28 (d, J=3.5 Hz, 1H), 6.39 (t, J=4.5 Hz, 1H), 7.18 (d, J=3.5 Hz, 1H), 7.32 (d, J=8.4 Hz, 2H) and 7.70 (d, J=8.4 Hz, 2H) ppm. IR (KBr) 2220, 1595, 1380, 1195, 1170, 1130, 820, 705, 665 and 595 cm^{-1}. Mass (m/z, %) 298 (M^+, 31), 155 (36), 143 (43), 142 (25) and 91 (100). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.35; H, 4,76; N, 9.35; S, 10.77.

4-Cyano-1-(p-toluenesulfonyl)-4,5-dihydroindole (8): Mp 123 - 124 °C (from toluene-pentane). NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.47 - 2.59 (m, 1H), 2.64 (dd, J=1.8 Hz, J=4.5 Hz, 1H), 3.86 (dd, J=9.2 Hz, J=9.6 Hz, 1H), 5.80 (dt, J=10.1 Hz, J=4.5 Hz, 1H), 6.29 (d, J=3.3 Hz, 1H), 6.92 (dt, J=10.1 Hz, J=1.8 Hz, 1H), 7.16 (d, J=3.3 Hz, 1H), 7.30 (d, J=8.4 Hz, 2H) and 7.70 (d, J=8.4 Hz, 2H) ppm. IR (KBr) 2250, 1595, 1370, 1180, 1140, 820, 720, 675 and 540 cm^{-1}. Mass (m/z, %) 298 (M^+, 23), 155 (51), 143 (13) and 91 (100). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4,73; N, 9.39; S, 10.75. Found: C, 64.39; H, 4.84; N, 9.40; S, 10.95.

4-Cyano-1-(p-toluenesulfonyl)indole (6) and 4-Cyano-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (9). A solution of 4-cyano-1-(p-toluenesulfonyl)-6,7-dihydroindole (7) (335 mg, 1.1 mmol) in cymene (5 ml) was heated to reflux with 5 % Pd-C (100 mg) for 2 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was chromatographed on a silica gel column with dichloromethane-hexane to give 4-cyano-1-(p-toluenesufonyl)indole (6) (148 mg, 44.5 %) and 4-cyano-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (9) (111 mg, 32.9 %).

4-Cyano-1-(p-toluenesulfonyl)indole (6): Mp 131.5 - 133 °C (from chloroform-hexane). NMR ($CDCl_3$) δ 2.34 (s, 3H), 6.85 (d, J=3.6 Hz, 1H), 7.24 (d, J=8.4 Hz, 2H), 7.34 (t, J=8.4 Hz, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.74 (d, J=3.6 Hz, 1H), 7.75 (d, J=8.4 Hz, 2H) and 8.23 (d, J=8.4 Hz, 1H) ppm. IR (KBr) 2270, 1595, 1420, 1380, 1365, 1180, 760 and 680 cm^{-1}. Mass (m/z, %) 296 (M^+, 20), 155 (52),

91 (100) and 65 (25). Anal. Calcd for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45; S, 10.82. Found: C, 64.57; H, 4.09; N, 9.41; S, 10.83.

4-Cyano-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (9): Mp 101.5 - 102.5 °C (purified by sublimation). NMR ($CDCl_3$) δ 1.67 - 2.13 (m, 4H), 2.40 (s, 3H), 2.70 (broad t, J=5.4 Hz, 2H), 3.67 (broad t, J=4.5 Hz, 1H), 6.24 (d, J=3.3 Hz, 1H), 7.22 (d, J=3.3 Hz, 1H), 7.30 (d, J=8.4 Hz, 2H) and 7.68 (d, J=8.4 Hz, 2H) ppm. Mass (m/z, %) 300 (M^+, 26), 155 (31), 145 (57), 118 (26) and 91 (100). Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 63.99; H, 5.39; N, 9.20; S, 10.52.

4-Cyano-1-(p-toluenesulfonyl)indole (6) from 5-Chloro-4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5b). 5-Chloro-4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5b) (1.27 g, 3.0 mmol) was heated with phosphorus oxychloride (1.38 g, 9.0 mmol) in pyridine (5 ml) at 100 °C for 5 h. Dichloromethane (50 ml) was added to the reaction mixture, and the solution was washed with 2 N HCl, water, saturated aq. NaCl solution, and dried over $MgSO_4$. The drying agent was removed by filtration and the filtrate was concentrated. The residue was chromatographed on a silica gel column with dichloromethane to give 4-cyano-1-(p-toluenesulfonyl)indole (6) (0.393 g, 44.2 %).

4-Cyano-1-(p-toluenesulfonyl)indole (6) from 5-Bromo-4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5c). 4-Cyano-1-(p-toluenesulfonyl)indole (6) (0.548 g, 61.6 %) was obtained from 5-bromo-4-cyano-1-(p-toluenesulfonyl)-4-trimethylsiloxy-4,5,6,7-tetrahydroindole (5c) (1.40 g, 3.0 mmol) following the same procedure as described above.

General Procedure for the Catalytic Dehydrogenation. A 3:1 mixture of 4-cyano-1-(p-toluenesulfonyl)-6,7-dihydroindole (7) and 4-cyano-1-(p-toluenesulfonyl)-4,5-dihydroindole (8) (250 mg, 0.84 mmol) was heated with 5 % Pd-C (25 mg) at refluxing temperature in 5ml of the solvent indicated in Table I for 2 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was chromatographed on a silica gel column with dichloromethane to give 4-cyano-1-(p-toluenesulfonyl)indole (6).

Oxidation with Cupric Chloride. A 3:1 mixture of 4-cyano-1-(p-toluenesulfonyl)-6,7-dihydroindole (7) and 4-cyano-1-(p-toluenesulfonyl)-4,5-dihydroindole (8)

(250 mg, 0.84 mmol) was heated with $CuCl_2$ (169 mg, 1.26 mmol) at refluxing temperature in 50% aqueous AcOH (5 ml) for 2 h. The solvent was removed and the residue was chromatographed on a silica gel column with dichloromethane to give 4-cyano-1-(p-toluenesulfonyl)indole (6) (109 mg, 43.8 %).

Oxidation with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone. A 3:1 mixture of 4-cyano-1-(p-toluenesulfonyl)-6,7-dihydroindole (7) and 4-cyano-1-(p-toluenesulfonyl)-4,5-dihydroindole (8) (178 mg, 0.60 mmol) was heated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (142 mg, 0.63 mmol) at 80 °C for 3 h. The solvent was removed and the residue was chromatographed on a silica gel column with dichloromethane to give 4-cyano-(p-toluenesulfonyl)indole (162 mg, 92.6 %).

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