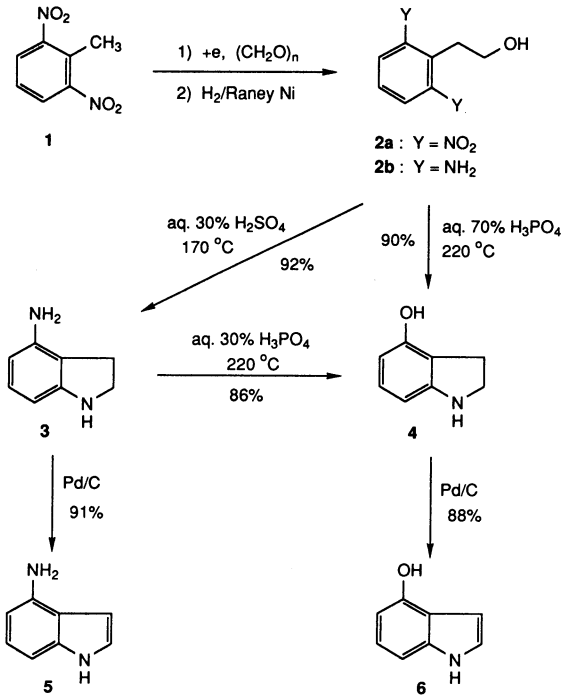
A Facile Synthesis of 4-Hydroxy- and 4-Aminoindoles through Corresponding Indolines

Hideo TANAKA, Yasuo MURAKAMI, Takao AIZAWA, and Sigeru TORII*
Department of Applied Chemistry, Faculty of Engineering,
Okayama University, Tsushima Naka, Okayama 700
(Received June 29, 1989)

Synopsis. 2-(2,6-Diaminophenyl)ethanol can be conducted to 4-hydroxyindoline under heating in aqueous 70% phosphoric acid, and to 4-aminoindoline under heating in aqueous 30% sulfuric acid. Both 4-hydroxy- and 4-aminoindoles were obtained by dehydrogenation of the indolines under refluxing in 1,4-dimethylbenzene over palladium on charcoal.

Indoles bearing an oxygen or nitrogen atom at the 4-position have been of interest for many years because of their potent and diverse therapeutical activities.[1] 4-Amino- and 4-hydroxyindoles (**5** and **6**) are used as versatile intermediates in the synthesis of therapeutical compounds. Most of electrophilic substitution reactions of indoles take place at the 4 and 7-positions and only the tactics reaching the desired 4-substituted indoles **5** and **6** have been required.[2,3] 4-Hydroxyindole (**6**) has been synthesized from 6-benzyloxy-2-nitrotoluene by one-carbon homologation with *N,N*-dimethylformamide dimethyl acetal and subsequent hydrogenative cyclization.[3d,e] 2,6-Dinitrotoluene (**1**) has also been used for the preparation of 4-hydroxyindole (**6**) via 4-aminoindole (**5**).[3f] In the practical sense, however, these procedures are not necessarily satisfactory, suffering insufficient overall yields and/or the use of the expensive chemicals. Herein, we describe a short-cut route to 4-amino- and 4-hydroxyindoles (**5** and **6**) from 2,6-dinitrotoluene (**1**), which involves 1) one-carbon homologation of **1** with formaldehyde followed by the hydrogenation (**2a**→**2b**) and 2) subsequent cyclization, giving the indoline **3**, or a one-pot cyclization-hydroxylation reaction, affording the indoline **4** (Scheme 1).



Scheme 1.

One-carbon homologation of 2,6-dinitrotoluene (**1**) with paraformaldehyde was successfully performed by the action of an electrochemically generated base (EG base). In the previous paper,[4] we have disclosed an EG base-induced hydroxymethylation of the side chain of 2-nitrotoluene with paraformaldehyde. The smooth extension of the method to **1** was verified by obtaining 2-(2,6-dinitrophenyl)ethanol (**2a**) in 94% yield after passage of a catalytic amount of electricity (0.06 F mol^{-1}) in a DMF-Et_4NOTs-$(CH_2O)_n$ system. Hydrogenation of **2a** over Raney Ni catalyst gave 2-(2,6-diaminophenyl)ethanol (**2b**) in 86% yield.

The conversion of **2b** into the 4-amino- and 4-hydroxyindolines (**3** and **4**) was performed by heating with proper acids, respectively (Scheme 1). The dehydrogenative cyclization of **2b** to **3** was achieved by heating in a sealed tube with an aqueous 30% sulfuric acid at 170 °C, affording 4-aminoindoline (**3**) in 92% yield. A similar result was obtained by heating of **2b** in an aqueous 1% phosphoric acid at 220 °C (86% yield).

The hydrolysis of the amino moiety of **3** was, at first, carried out by the conventional diazotization-hydrolysis reaction with sodium nitrate in aqueous 60% sulfuric acid (Method A). The satisfactory yields (>77%) were only achieved under high dilution conditions (<1%). When the concentration of **3** rose up to 3%, the yield of **4** decreased to less than 65%. Consequently, we turned our attention to the hydrolysis of 4-aminoindoline (**3**) to 4-hydroxyindoline (**4**) by heating with acids (Method B). The results obtained with various acids are shown in Table 1. Among the

Table 1. Effect of Acid in the Hydrolysis of 4-Aminoindoline (**3**) to 4-Hydroxyindoline (**4**)[a]

Entry	Acid	Yield of **4** %[b]	Recovered **3** %[b]
1	H_3PO_4	86	3
2	H_2SO_4	23	72
3	HCl	30	60
4	H_3BO_4	7	70
5	NaH_2PO_4	Trace	72
6	$NaHSO_3$	—[c]	—
7	None	—	93

a) Carried out with **3** (2.2 mmol) in aqueous 30% acids (6 g) at 220 °C for 24 h. b) Isolated yields. c) A complex mixture of decomposition products was formed.

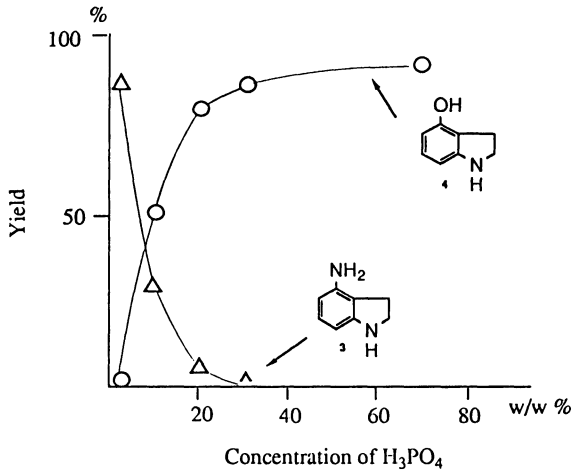


Fig. 1. Effect of concentration of H_3PO_4 on the conversion of 2-(2,6-diaminophenyl)ethanol (**2b**) into 4-amino and 4-hydroxyindolines (**3** and **4**). All experiments were carried out with **2b** (2 mmol) in aqueous H_3PO_4 (6 g) at 220 °C for 24 h.

acids, aqueous 30% phosphoric acid is the best choice, affording the desired product **4** in 86% yield (Entry 1), while sulfuric acid, hydrochloric acid, and boric acid are less effective (Entries 2—4). Sodium dihydrogenphosphate and sodium hydrogensulfite are not feasible for the present purpose (Entries 4 and 5).

As mentioned above, aqueous phosphoric acid is effective both for cyclization of **2b** into 4-aminoindoline (**3**) and for hydrolysis of **3** into 4-hydroxyindoline **4**. This finding, in turn, spurred us to examine a one-pot transformation of 2-(2,6-diaminophenyl)-ethanol (**2b**) into 4-hydroxyindoline (**4**) by heating with an aqueous 1—70% phosphoric acid at 220 °C. As illustrated in Fig. 1, the distribution of the products **3** and **4** was highly dependent on the concentration of phosphoric acid. In fact, the exclusive conversion to **4** was attained with aqueous 70% phosphoric acid.

The 4-substituted indolines **3** and **4** can be readily converted to the corresponding indoles **5** (91%) and **6** (88%) by heating to reflux in *p*-xylene over palladium on charcoal.[5,6] As an alternative route to **6**, hydrolysis of **5** was also attempted under the same conditions as for the hydrolysis of **3**, but all the trials resulted in the formation of a complex mixture.

In conclusion, the preparation of 4-amino- and 4-hydroxyindoles (**5** and **6**) from 2,6-dinitrotoluene (**1**) has been achieved in satisfactory overall yields (64—67%). Further transformation of **5** and **6** into the useful therapeutical compounds are in progress.

Experimental

IR spectra were recorded on a JASCO IRA-1 grating spectrometer and ^1H NMR spectra were measured at 60 MHz with a Hitachi R-24 spectrometer. Chemical shifts are expressed in parts per million downfield from Me_4Si as an internal reference. Melting points are uncorrected. Column chromatography was carried out on Wako gel C-200 (silica gel) with hexane–EtOAc as an eluent.

2-(2,6-Dinitrophenyl)ethanol (2a): Into both anode and cathode compartments of an H-shaped divided cell[4] was placed a DMF solution of Et_4NOTs (420 mg/8 ml each). To the cathode compartment were added 2,6-dinitrotoluene (**1**) (1.04 g, 5.7 mmol) and $(CH_2O)_n$ (220 mg, 7.3 mmol on the basis of formaldehyde). The mixture was electrolyzed under a constant current of 3.3 mA cm^{-2} at room temperature for 50 min (0.06 F mol^{-1}). The catholytes were poured into aqueous 5% HCl and extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed to afford **2a**[5b] (1.14 g, 94%): mp 69—71 °C; ^1H NMR ($CDCl_3$) δ=2.05 (1H, s, OH), 3.27 (2H, t, J=6 Hz, $ArCH_2$), 3.90 (2H, t, J=6 Hz, CH_2O), 7.35—8.05 (3H, m, ArH); IR ($CHCl_3$) 3600, 3010, 2885, 1540, 1365, 1050, 910, 705 cm^{-1}.

2-(2,6-Diaminophenyl)ethanol (2b): To a stirred suspension of Raney Ni (W-2, 12.5 g) in MeOH (80 ml) was added at 55—65 °C a solution of 2-(2,6-dinitrophenyl)ethanol (**2a**) (40 g, 0.19 mol) in methanol (180 ml) over a period of 2 h under H_2 atmosphere (5—9 atm). After stirring for additional 2 h, the catalysts were removed by filtration and washed with methanol. The filtrate and washings were combined and concentrated in vacuo. The residue was recrystallized from ethanol to give **2b**[7] (24.7 g, 86%): mp 109—110 °C; ^1H NMR (acetone-d_6) δ=2.63 (2H, t, J=6 Hz, $ArCH_2$), 3.65 (2H, t, J=6 Hz, CH_2O), 4.03 (5H, br s, NH_2, OH), 5.9—6.7 (3H, m, ArH); IR (Nujol) 3370, 3200, 1595, 1463, 1050, 858, 733 cm^{-1}.

4-Aminoindoline (3): 2-(2,6-Diaminophenyl)ethanol (**2b**) (300 mg, 1.97 mmol) and 30% aqueous sulfuric acid (6 g) were charged to a sealed tube and heated at 170 °C for 24 h. The acidic solution was neutralized with aqueous 40% NaOH and extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed to give **3**[5b] (245 mg, 92%): mp 44—45 °C; ^1H NMR ($CDCl_3$) δ=2.79 (2H, t, J=8 Hz, $ArCH_2$), 3.1—3.7 (5H, m, CH_2N, NH, NH_2, CH_2N), 5.95 (1H, d, J=8 Hz, ArH), 6.0 (1H, d, J=8 Hz, ArH), 6.7 (1H, t, J=8 Hz, ArH); IR (CH_2Cl_2) 3360, 1633, 1500, 1485, 1315, 1065 cm^{-1}.

4-Hydroxyindoline (4): Method A. To a solution of 4-aminoindoline (**3**) (112 mg, 0.83 mmol) in 70% aqueous H_2SO_4 (11 g) was added 4% aqueous $NaNO_2$ (1.5 ml, 1.0 equiv) at 0—10 °C over a period of 1 h. After stirring at 0—5 °C for 10 h, sulfamic acid (10 mg) was added. The stirring was continued at room temperature for 1 h and at 65—75 °C for additional 4 h. The acidic solution was neutralized with 10% aqueous 40% NaOH and extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to give **4** (86 mg, 77%): mp 139—140 °C (lit,[2c] mp 147 °C).

Method B: 4-Aminoindoline (**3**) (300 mg, 2.24 mmol) and 30% aqueous phosphoric acid (3 g) were charged to a sealed tube. The mixture was heated at 220 °C for 24 h and then cooled to room temperature. The acidic solution was neutralized with aqueous 40% NaOH, extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed to afford **4** (260 mg, 86%), whose IR and ^1H NMR spectra are identical with those of **4** obtained above.

Direct Conversion of 2-(2,6-Diaminophenyl)ethanol (2b) to 4-Hydroxyindoline (4): A mixture of 2-(2,6-diaminophenyl)ethanol (**2b**) (300 mg, 1.97 mmol) and 70% aqueous phosphoric acid (3 g) was charged to a sealed tube and heated at 220 °C for 24 h. The mixture was worked up in a similar manner to that described above to give **4** (240 mg, 90%), whose IR and ^1H NMR spectra are identical with those of **4** obtained above.

4-Hydroxyindole (5): A mixture of 4-hydroxyindoline (**4**)

(68 mg, 0.51 mmol) and 10% Pd/C (10 mg), in *o*-xylene (10 ml) was heated to reflux for 2.3 h under N_2 atmosphere. Usual workup of the mixture afforded **5** (59 mg, 88%): mp 98—98.6 °C (lit,[3b] 96—98 °C); ^{1}H NMR (acetone-d_6) δ= 6.3—7.2 (5H, m, ArH, CH=CHN), 8.1 (1H, s, OH), 9.8 (1H, br s, NH); IR (CH_2Cl_2) 3550, 3435, 1590, 1500, 1450, 1355, 1075, 690 cm^{-1}.

4-Aminoindole (6): A mixture of 4-aminoindoline (**3**) (70 mg, 0.52 mmol) and 10% Pd/C (10 mg) in *p*-xylene (2.0 ml) was heated to reflux for 3 h under N_2 atmosphere. Usual workup of the mixture afforded **6** (63 mg, 91%): mp 104—105 °C (lit,[3d] mp 106—108 °C); ^{1}H NMR ($CDCl_3$) δ=3.76 (2H, br s, NH_2), 6.17—7.06 (5H, m, ArH, C=CH-N, ArCH=C), 7.95 (1H, br s, NH); IR (CH_2Cl_2) 3440, 3350, 1618, 1587, 1500, 1405, 1364 cm^{-1}.

References

1) For review: R. J. Sundberg, "Chemistry of Indoles," Academic Press, New York (1970); R. T. Brown, J. A. Joule, and P. G. Sammes, "Comprehensive Organic Chemistry," ed by D. H. R. Barton and W. D. Ollis, Pergamon Press, Oxford (1979), Vol. 4, p. 411; J. E. Saxton, "Indoles," Wiley-Interscience, New York (1983), Part IV.

2) The radical hydroxylation of indoles with hydrogen peroxide, affording a mixture of 4-, 5-, 6-, and 7-hydroxyindoles has been reported: a) J. Gartz, *Pharmazie*, **40**, 356 (1985); b) C. Berrier, J. C. Jacquesy, and M. P. Jouannetaud, and A. Renoux, *Tetrahedron Lett.*, **27**, 4565 (1986); c) *idem*, *New J. Chem.*, **11**, 605 (1987).

3) a) A. Stoll, F. Troxler, J. Peyer, and A. Hofmann, *Helv. Chim. Acta*, **38**, 1452 (1955); b) D. B. Repke, W. J. Ferguson, and D. K. Bates, *J. Heterocycl. Chem.*, **14**, 71 (1977); c) S. Torii, K. Uneyama, T. Onishi, Y. Fujita, M. Ishiguro, and T. Nishida, *Chem. Lett.*, **1980**, 1603; d) L. I. Kruse, *Heterocycles*, **16**, 1119 (1981); e) M. Somei, S. Inoue, S. Tokutake, F. Yamada, and C. Kaneko, *Chem. Pharm. Bull.*, **29**, 726 (1981); f) M. Somei and M. Tsuchiya, *ibid.*, **29**, 3145 (1981); g) R. D. Clark and D. B. Repke, *Heterocycles*, **22**, 195 (1984); h) M. Matsumoto and N. Watanabe, *ibid.*, **22**, 2313 (1984); i) M. Matsumoto, Y. Ishida, and N. Watanabe, *ibid.*, **23**, 165 (1985); j) A. D. Batcho and W. Leimgruber, *Org. Synth.*, **63**, 214 (1985); k) M. E. Krolski, A. F. Renaldo, D. E. Rudisill, and J. K. Stille, *J. Org. Chem.*, **53**, 1170 (1988); and references cited therein.

4) S. Torii, Y. Murakami, H. Tanaka, and K. Okamoto, *J. Org. Chem.*, **51**, 3143 (1986).

5) a) R. R. Hunt and R. L. Rickard, *J. Chem. Soc. C*, **1966**, 344; b) J. Bakke, *Acta Chem. Scand., Ser. B*, **28**, 134 (1974).

6) Direct transformation of 2-(6-halo-2-aminophenyl)-ethanols into 4-haloindoles has been performed by heating with ruthenium catalysts: T. Tsuji, K. T. Huh, Y. Yokohama, and Y. Watanabe, *J. Chem. Soc., Chem. Commun.*, **1986**, 1575.

7) S. T. Rashevskaya, E. S. Kashcheeva, and E. I. Mostoslavskaya, *Zh. Obshch, Khim.*, **33**, 3998 (1963); *Chem. Abstr.*, **60**, 9178e (1964).