Expedient Synthesis of 5,6-Dihydroxyindole and Derivatives via an Improved Zn(II)-Assisted 2,β-Dinitrostyrene Approach

Luisa Novellino, Marco d'Ischia, Giuseppe Prota*

Department of Organic and Biological Chemistry, University of Naples «Federico II», Via Mezzocannone 16, I-80134 Naples, Italy
Fax +39(81)5521217; E-mail: prota@cds.unina.it

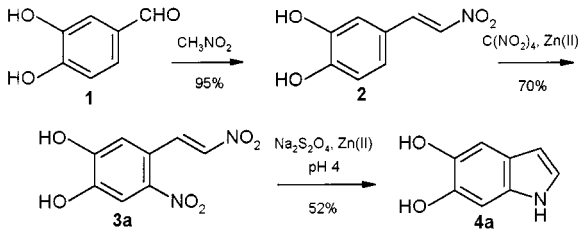
Received 1 November 1998

Abstract: A facile 3-step synthesis of 5,6-dihydroxyindole (**4a**) is reported, featuring the Zn(II)-controlled regioselective nitration of 3,4-dihydroxynitrostyrene (**2**) with tetranitromethane at pH 8.0, and the reductive cyclization of the resulting 4,5-dihydroxy-2,β-dinitrostyrene (**3a**) with $Na_2S_2O_4$/Zn(II) at pH 4. The latter procedure was successfully extended to the conversion of the 2,β-dinitrostyrenes **3b** and **3c** to 5,6-dibenzyloxyindole (**4b**) and 5,6-diacetoxyindole (**4c**) in good-to-high yields.

Key words: 5,6-dihydroxyindoles, 2,β-dinitrostyrenes, regioselective nitration, tetranitromethane, Zn(II) ions, sodium dithionite

5,6-Dihydroxyindole (**4a**) and its congeners currently represent an attractive synthetic focus because of their central role in mammalian melanin pigmentation[1] and their increasing exploitation as active ingredients in innovative dermocosmetic formulations.[2] Additional impetus for studies of 5,6-dihydroxyindoles has stemmed from the recent recognition of their outstanding free radical scavenging and (photo)protective capabilities,[3] warranting ranking among the most potent endogenous antioxidants.[4] To fully exploit the expanding range of opportunities offered by **4a** and its derivatives, e.g. 5,6-dibenzyloxyindole (**4b**) and 5,6-diacetoxyindole (**4c**), requires access to synthetic methodology capable of circumventing difficulties posed by the marked instability of **4a** and its derivatives to acids, alkali and oxidants,[5] which hampers chromatography, crystallization and other purification procedures, and accounts for extensive polymerization during preparation and workup.

Of the several strategies that have been devised for the preparation of **4a** and its congeners,[6–15] the most convenient ones hinge on the classical 2,β-dinitrostyrene approach exemplified by the popular Benigni and Minnis[8] scheme. In spite of substantial modifications and refinements[10–12,14] available, 2,β-dinitrostyrene-based routes to 5,6-dihydroxyindole derivatives still suffer from a number of drawbacks, including tedious and cumbersome protection/deprotection steps, lengthy synthetic sequences (up to 2 days), poorly reproducible cyclization yields, and need for product purification, e.g. by HPLC or column chromatography, which discourage application to routine laboratory preparations. In this paper we report the realization of a straightforward 3-step synthesis of **4a** (Scheme 1) in which protection-deprotection steps have been circumvented for the first time through expedient use of catalysts and careful selection of reaction conditions. The novel methodology capitalizes on the Zn(II)-assisted regioselective nitration of 3,4-dihydroxy-β-nitrostyrene (**2**) and features an improved procedure for the reductive cyclization of 4,5-dihydroxy-2,β-dinitrostyrene (**3a**), which has been conveniently extended to the syntheses of **4c** and **4b** from the appropriate 2,β-dinitrostyrene precursors.



Scheme 1

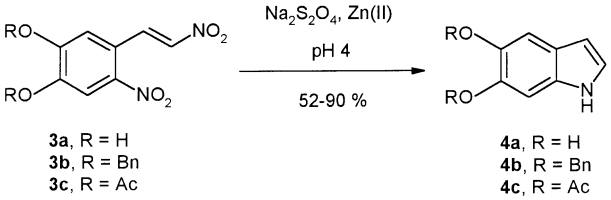
The first intermediate in the process, the nitrostyrene **2**, was readily prepared in excellent yield by Henry condensation of 3,4-dihydroxybenzaldehyde (**1**) with nitromethane. Regioselective nitration of **2** to **3a**, however, was anticipated to be difficult because of the presence of the sensitive *o*-dihydroxy functionality, which accounts for a marked susceptibility of the substrate to oxidative polymerization and orients attack of nitrating agents largely *ortho* to the hydroxyl groups.[11] Indeed, under classical nitration conditions,[16] tarry materials were invariably obtained, and the main isolable product was 3,4-dihydroxy-2,β-dinitrostyrene,[17] the desired regioisomer **3a** being formed in comparably low amounts.

The problems accompanying nitration of **2** have long been known[11] and have traditionally been overcome by derivatization with suitable alkyl groups to protect the catechol functionality. As an expedient alternative to this time-consuming *O*-alkylation step, we envisaged the possibility that engaging **2** in chelate formation with transition metal ions under mild alkaline conditions could hinder electrophilic attack of nitrating agents *ortho* to the phenolic groups and direct reactivity to the distal 6-position. In line with this expectation, reaction of **2** with tetranitromethane (TNM)[18] in ethanol/0.1 M $NaHCO_3$ buffer (pH 8) at 0°C for 40 minutes in the presence of Zn(II) ions resulted in the smooth formation of **3a** in 70% yield. As obtained, the product was sufficiently pure for further use without purification. In the absence of Zn(II) ions, 3,4-dihydroxy-2,β-dinitrostyrene was again the main regioisomer. Other met-

al ions, including Ni (II), Cu (II), Co (II), proved also capable of promoting nitration of **2** to **3a**, although less efficiently than Zn(II). The regiochemical control induced by Zn(II) is apparently unprecedented in the field of phenol/catechol nitration, and its actual scope and generality are currently under investigation.

Reductive cyclization of **3a** to **4a**, the last step in the planned synthetic sequence, required likewise use of reagents compatible with the marked instability imparted to substrate and product by the catechol functionality. Ruling out the Fe/HOAc[8] and other harsh reductive procedures,[19] the only attractive methodology for preparation of **4a** was catalytic hydrogenation over Pd/C.[10] In our hands, however, this procedure proved not entirely satisfactory, leading to poorly reproducible yields of **3a** often in a rather impure form. An additional limitation was envisioned in the incompatibility with hydrogenolyzable functionalities, such as benzyl groups, which precluded application to the reduction of 4,5-dibenzyloxy-2,β-dinitrostyrene (**3b**).[8] In seeking a more general reductive procedure, we therefore considered reagents operating at slightly acidic pH, with the dual scope of increasing susceptibility of nitro groups to reduction and limiting autoxidation of the resulting indole. After extensive screenings, we eventually found that **4a** could be obtained in 52% yield by treatment of **3a** with sodium dithionite in 0.1 M phosphate buffer (pH 4) at 40°C under Ar in the presence of Zn(II) ions, to form in situ ZnS_2O_4.[20] Use of Zn(II) ions proved critical, since little or no **4a** was formed at slightly acidic pH in the absence of added metal. Attempts to improve the yields of **4a** were thwarted by intrinsic difficulties in the cyclization of the unprotected dihydroxy compound, nor could we find other reagents effective enough to compete with the $Na_2S_2O_4$/Zn(II) system. The method was reproducible from a 100 mg scale to a 20 g scale and afforded a product of remarkable purity, within the limitations posed by its pronounced instability.

Interestingly, the $Na_2S_2O_4$/Zn(II) reduction procedure could conveniently be extended to the synthesis of some derivatives of **4a,** i.e. **4b** and **4c**, from the corresponding 2,β-dinitrostyrenes **3b** and **3c** (Scheme 2) in moderate-to-excellent yields (Table).



3a, R = H
3b, R = Bn
3c, R = Ac

4a, R = H
4b, R = Bn
4c, R = Ac

Scheme 2

The described formation of pure **4b** from **3b** represents a considerable improvement compared to the Fe/HOAc procedure of the Benigni and Minnis scheme,[8] because of the substantially increased product yield and alleviated time-consuming chromatographic purification. The efficient reductive cyclization of **3c** was likewise of practical interest, since it allowed a shorter access to **4c** in 4 steps and 44% overall yield.[21] In this case, use of a biphasic system consisting of 0.1 M phosphate buffer (pH 4) and dichloromethane was essential to prevent deacetylation of both substrate and product by the nucleophilic $S_2O_4^{2-}$ ions.

In summary, we have developed a streamlined 2,β-dinitrostyrene route to **4a** which represents a considerable achievement in terms of rapidity and product purity, two most critical problems in available syntheses of **4a**. The methodology is superior to previously reported procedures in that it: a) leads to pure product in only 3 steps and in 35% overall yield, against, e.g., a 21% overall yield by the Benigni and Minnis procedure; b) does not require troublesome protection-deprotection steps, lengthy reaction sequences or tedious chromatographic purifications; and c) is suitable for relatively large scale preparations. Chemical highlights of the work reported herein include exploitation of Zn(II) ions to achieve regiochemical control over TNM nitration of a catechol substrate and to enhance reactivity of $Na_2S_2O_4$ toward 2,β-dinitrostyrenes under acidic conditions.

All commercial reagents and solvents were used without further purification. Tetranitromethane (TNM) was purchased from Aldrich. NMR spectra were recorded in acetone-d_6 or in CD_3OD on a 200 MHz spectrometer. Mps were determined on a hot stage apparatus without correction.

Table Reductive Cyclization of 2,β-Dinitrostyrenes **3a–c** with the $Na_2S_2O_4$/Zn(II) System.

Substrate	Solvent	Reaction time (min)		Product	Yield[a] (%)	mp (°C)	
		Temp (°C)	Time (h)			found	reported
3a	0.1 M phosphate buffer, pH 4	40	20	**4a**	52	141–142[b]	141–142[8]
3b	EtOH / 0.1 M phosphate buffer, pH 4	50	180	**4b**	90	114	115[8]
3c	CH_2Cl_2 / 0.1 M phosphate buffer, pH 4	45	240	**4c**	70	132[b]	134–136[12]

[a] Isolated yield, mean of 3 preparations (S.D ± 4 %).
[b] Not crystallized.

(*E*)-3,4-Dihydroxy-β-nitrostyrene (2)
A mixture of **1** (20 g, 0.145 mol), NH_4OAc (44.6 g, 0.57 mol), $MeNO_2$ (53 g, 0.87 mol) in HOAc (200 mL) was refluxed for 25 min. The solvent was then evaporated in a vacuum to give a dark red oily residue, which was taken up in H_2O (50 mL) and repeatedly extracted with Et_2O (3 × 100 mL). Evaporation of the organic phase gave **2** as bright orange crystals (25 g, 95%), mp 131.9–132.2°C.

^{1}H NMR (acetone-d_6): δ = 6.96 (d, 1 H, *J* = 8.4 Hz), 7.25 (dd, 1 H, *J* = 8.4, 2.0 Hz), 7.31 (d, 1 H, *J* = 2.0 Hz), 7.77 (d, 1 H, *J* = 13.6 Hz), 7.98 (d, 1 H, *J* = 13.6 Hz).

^{13}C NMR (acetone-d_6) δ = 116.4, 116.7, 123.3, 124.7, 135.8, 140.4, 146.7, 150.6.

HRMS (FAB): *m*/*z* calcd for $C_8H_8NO_4$ (M+H$^+$) 182.0453, found 182.0460.

Anal. calcd for $C_8H_7NO_4$: C, 53.04; H, 3.95; N, 7.72. Found: C, 53.09; H, 3.89; N, 7.75.

(*E*)-4,5-Dihydroxy-2,β-dinitrostyrene (3a)
To a mixture of **2** (10 g, 0.055 mol) and $ZnSO_4$ (79 g, 0.275 mol) in 0.1 M $NaHCO_3$ buffer, (pH 8, 400 mL) and EtOH (80 mL) at 0°C (ice bath) was added dropwise a solution of TNM (16.2 g, 0.08 mol) in EtOAc (300 mL). The mixture was stirred in an ice bath for 40 min and then was concentrated under reduced pressure at r.t. to remove most of the EtOH. The residue was acidified to pH 4 and repeatedly extracted with Et_2O (3 × 200 mL). Hexane was added to the dried (Na_2SO_4) organic phase to precipitate an orange solid which was recrystallized from H_2O to yield **3a** (8.75 g, 70%) as bright yellow needles, mp 171–172°C (Lit.[11] mp 169–171°C).

^{1}H NMR (CD_3OD): δ = 7.27 (s, 1 H), 7.69 (s, 1 H), 7.75 (d, 1 H, *J* = 13.4 Hz), 8.50 (d, 1 H, *J* = 13.4 Hz).

HRMS (FAB): *m*/*z* calcd for $C_8H_7N_2O_6$ (M+H$^+$) 227.0304, found 227.0301.

Anal. calcd for $C_8H_6N_2O_6$: C, 42.48; H, 2.68; N, 12.39. Found: C, 42.56; H, 2.71; N, 12.33.

CAUTION: adviceable use of TNM suggests handling under an efficient hood.

5,6-Dihydroxyindole (4a)
A stirred mixture of **3a** (8.0 g, 0.035 mol) in 0.1 M phosphate buffer (pH 4, 100 mL) in a three-necked round-bottom flask, and a solution of $Na_2S_2O_4$ (60.9 g, 0.35 mol) and $ZnSO_4$ (50.3 g, 0.175 mol) in 0.1 M phosphate buffer (pH 4, 100 mL) were fluxed with Ar separately for 1 h. The latter solution was then rapidly added to the former via a dropping funnel and the resulting mixture was stirred under Ar for 20 min at 40°C. Eventually, it was extracted with EtOAc (3 × 100 mL) under Ar and the combined extracts were carefully dried (Na_2SO_4). Addition of benzene caused precipitation of **4a** as a pale yellow solid (2.7 g, 52%; > 98 % purity as determined by TLC and NMR); mp 141–142°C (Lit.[8] mp 141–142 °C).

^{1}H NMR (acetone-d_6) δ = 6.23 (m, 1H), 6.89 (d, 1 H, *J* = 1 Hz), 6.98 (s, 1 H), 7.06 (dd, 1 H, *J* = 8.0, 6.0 Hz).

HRMS (EI): *m*/*z* calcd for $C_8H_7NO_2$ (M$^+$) 149.0477, found 149.0489.

Anal. calcd for $C_8H_7NO_2$: C, 64.42; H, 4.74; N, 9.39. Found: C, 64.51; H, 4.79; N, 9.33.

NOTE: Failure to thoroughly deoxygenate and/or desiccate the organic extracts often resulted in darkening and more or less extensive polymerization of the product with markedly decreased yield.

5,6-Dibenzyloxyindole (4b)
To a stirred mixture of **3b**[8] (10 g, 0.025 mol) in EtOH (200 mL) at 50°C was added a solution of $Na_2S_2O_4$ (65.2 g, 0.375 mol) and $ZnSO_4$ (57.5 g, 0.2 mol) in 0.1 M phosphate buffer (pH 4, 200 mL). The mixture was stirred for 3 h at 50°C and then was concentrated under reduced pressure at r.t. to remove most of the EtOH. The residue was extracted with EtOAc (3 × 100 mL), dried (Na_2SO_4) and treated with hexane to precipitate **4b** as a pale yellow solid which was recrystallized from benzene/hexane (7.4 g, 90%); mp 114°C (Lit.[8] mp 115°C).

^{1}H NMR (acetone-d_6) δ = 5.10 (s, 2 H), 5.12 (s, 2 H), 6.29 (m, 1 H), 7.08 (s, 1 H), 7.12 (m, 1 H), 7.19 (s, 1 H), 7.33 (m, 6 H), 7.50 (m, 4 H).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{19}NO_2$ (M$^+$) 329.1417, found 329.1420.

Anal. calcd for $C_{22}H_{19}NO_2$: C, 80.21; H, 5.82; N, 4.25. Found: C, 80.29; H, 5.85; N, 4.21.

5,6-Diacetoxyindole (4c)
To a solution of **3c**[12] (10 g, 0.032 mol) in CH_2Cl_2 (500 mL) was added a solution of $Na_2S_2O_4$ (83.5 g, 0.48 mol) and $ZnSO_4$ (73.6 g, 0.26 mol) in 0.1 M phosphate buffer (pH 4, 500 mL). The mixture was stirred under Ar at 45°C for 4 h. After cooling to r.t., the organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic phases were dried (Na_2SO_4), concentrated under reduced pressure at r.t. and treated with hexane to precipitate **4c** as a chromatographically homogenous greyish solid (5.2 g, 70 %); mp 132°C (Lit.[12] mp 134–136°C).

^{1}H NMR (acetone-d_6) δ = 2.20 (s, 3 H), 2.22 (s, 3 H), 6.43 (m, 1 H), 7.23 (br s, 1 H), 7.32 (s, 1 H), 7.33 (m, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{11}NO_4$ (M$^+$) 233.0868, found 233.0869.

Anal. calcd for $C_{12}H_{11}NO_4$: C, 61.79; H, 4.76; N, 6.01. Found: C, 61.81; H, 4.73; N, 6.06.

Acknowledgement

This work was supported by grants from MURST (Rome) and Lawrence M. Gelb Research Foundation (Stamford, CT). We thank Miss Silvana Corsani for technical assistance.

References

(1) Prota, G. *Melanins and Melanogenesis*, Academic Press: San Diego, 1992.
Prota, G. *Fortschr. Chem. Organ. Naturstoffe* **1995**, *64*, 93.
(2) Prota, G.; Brown, K. *Cosmetics & Toiletries* **1994**, *109*, 59.
Prota, G. *Cosmetics & Toiletries* **1996**, *111*, 43.
(3) Memoli, S.; Napolitano, A.; d'Ischia, M.; Misuraca, G.; Palumbo, A.; Prota, G. *Biochim. Biophys. Acta* **1996,** *1346*, 61.
(4) Prota, G.; Misuraca, G. In *Melanogenesis and Malignant Melanoma: Biochemistry, Cell Biology, Molecular Biology, Pathophysiology, Diagnosis and Treatment*; Hori, Y.; Hearing, V.J.; Nakayama, J., Eds.; Elsevier: Amsterdam, 1996; p 49.
(5) d'Ischia, M.; Napolitano, A.; Prota, G. *Gazz. Chim. Ital.* **1996,** *126*, 783.
Manini, P.; d'Ischia, M.; Milosa, M.; Prota, G. *J. Org. Chem.* **1998**, *63*, 7002.
(6) Beer, R.J.; Clarke, K.; Khorana, H.G.; Robertson, A. *J. Chem. Soc.* **1948**, 2223.
(7) Walker, G.N. *J. Am. Chem. Soc.* **1954**, *77*, 3844.
(8) Benigni, J.D.; Minnis, R.L. *J. Heterocycl. Chem.* **1965**, *2*, 387.
(9) Lutz, W.B.; McNamara, C.R.; Olinger, M.R.; Schmidt, D.F.; Doster, D.E.; Fiedler, M.D. *J. Heterocyclic Chem.* **1984**, *21*, 1183.
(10) Murphy, B.P.; Schultz, T.M. *J. Org. Chem.* **1985**, *50*, 2790.

(11) Murphy, B.P.; Banks, H.D. *Synth. Commun*. **1985**, *15*, 321.
Mayer, A. A.; Murphy, B. P. *Synth. Commun*. **1985**, *15*, 423.
(12) Murphy, B.P. *J. Org. Chem.* **1985**, 50, 5873.
(13) Lim, M.I.; Patil, D.G. *Tetrahedron Lett.* **1987**, *28*, 3775.
(14) Rogers, C.B.; Blum, C.A.; Murphy, B.P. *J. Heterocycl. Chem.* **1987**, *24*, 941.
(15) Wakamatsu, K.; Ito, S. *Anal. Biochem.* **1988**, *170*, 335.
(16) Askani, R.; Taber, D.F. In *Comprehensive Organic Synthesis;* Trost, B.M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 104.
(17) 3,4-Dihydroxy-2,β-dinitrostyrene: red oil.
^{1}H NMR (CD_3OD): δ = 6.94 (d, 1 H, *J* = 8.5 Hz), 7.21 (d, 1 H, *J* = 8.5 Hz), 7.67 (d, 1 H, *J* = 13.4 Hz), 7.77 (d, 1 H, *J* = 13.4 Hz).
HRMS (FAB). *m*/*z* calcd for $C_8H_7N_2O_6$ ($M+H^+$) 227.0304, found 227.0310.
(18) Patterson, J.M. *J. Org. Chem.* **1955**, *20*, 1277.
(19) Sundberg, R. J. *The Chemistry of Indoles*. Academic Press: New York, 1970; p 142.
(20) ZnS_2O_4 has a maximum reducing capacity at pH 4–5, whereas under the same conditions $Na_2S_2O_4$ is much less efficient and tends to decompose. See: Fieser, L.F.; Fieser, M. *Reagents for organic synthesis*; Wiley: New York, 1967; Vol. 1, p 1294.
(21) The best reported route to **4c**[12] proceeded in 7 steps and 63% overall yield.

Article Identifier:
1437-210X,E;1999,0,05,0793,0796,ftx,en;H11098SS.pdf