An Efficient Synthesis of 2,5-Diamino-1,4-benzoquinone

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Abstract: A novel and efficient synthesis of 2,5-diamino-1,4-benzoquinone is described. The reaction involves a palladium/charcoal hydrogenolysis as the key step and provides the desired product in only four steps and very good overall yield.

Key words: palladium-on-charcoal, hydrogenolysis, 2,5-diamino-3,6-dibromoquinone, terreusinone

Synthesis of natural products is a challenge to organic chemists. Recently, marine microorganisms have proven to be a rich source for structurally novel natural products required for developing fine chemical agents. The natural product terreusinone \(\{2,6\text{-bis[(1R)-1-hydroxyisobutyl]}-1H,5H\text{-pyrrolo[2,3-b]indole-4,8-dione}\}\) (Figure 1), isolated from the marine algicolous fungus \(\text{Aspergillus terreus}\), was detected to possess UV-A absorbing activity with an ED\(_{50}\) value of 70 \(\mu\)g/mL.\(^1\) 2,5-Diamino-1,4-benzoquinone (Fragment 1) is an integral structure of naturally occurring biologically active compounds\(^1\) such as benzoquinonium chloride (Figure 2), a skeletal muscle relaxant.\(^{2a,b}\) It is a useful intermediate for the preparation of many industrial dyestuffs\(^3a\) and finds application in cross-linking and alkylation of DNA by aziridinylquinone.\(^3b\) Classical 2,5-diamino-1,4-benzoquinone (I) syntheses involve (i) reduction of 2,5-diazido-1,4-benzoquinone with sodium borohydride in ethanol to furnish I in 62% yield (path a),\(^4\) or (ii) disproportionation and reduction of 2,5-diazido-1,4-benzoquinone (a highly explosive compound) with sodium borohydride in ethanol to give I in 31% yield (path b), or (iii) reaction of ammonia with 2,5-dimethoxy-1,4-benzoquinone\(^5\) (path c) (Scheme 1). Derivatives of I are prepared by the oxidation of appropriate amines or alcohols,\(^6a\) and nuclear amination of 1,4-hydroquinones with aromatic amines catalyzed by fungal laccases (EC 1.10.3.2) from \(\text{Trametes sp.}\) and \(\text{Myceliophthora thermophila}.\(^{6b}\) These classical methods involve intermediates that are highly explosive or not-so-easy to synthesize. The present work describes a novel and efficient method for the synthesis of 2,5-diamino-1,4-benzoquinone (I) based on the hydrogenolysis of 2,5-diamino-3,6-dibromoquinone over palladium-on-charcoal.

[Figure 1: terreusinone and its fragments]

[Figure 2: Structure of benzoquinonium chloride]

Scheme 1 Reagents and conditions: (a) EtOH, excess NaBH\(_4\), 20 °C; (b) (i) acetone; (ii) EtOH, excess NaBH\(_4\), 20 °C; (c) EtOH, aq NH\(_3\), 80 °C, 1 h.

In continuation of our program on the syntheses of natural products, we attempted the synthesis of terreusinone having a dipyrrolo-1,4-benzoquinone moiety. In the literature
only a few methods are available for the synthesis of dipyralo-1,4-benzoquinones. These are, (i) synthesis of 1,5-bis(4-hydroxyphenyl)pyrrolo[2,3/f]benzopyrro-4,8-dione (2a) from 2,5-bis(4-hydroxyphenyl)amine-3,6-dibromo-1,4-benzoquinone (3a) and ethyl acetocetate in refluxing DMF using catalytic amounts of triethylamine\(^{7}\) (Scheme 2), and (ii) a low-yielding pyrolysis of the diketopiperazine 4c at 950 °C to give dipyralo-1,4-benzoquinone (2c)\(^{9}\) (Scheme 2).

In our efforts to synthesize the terreusinone analogue we followed the procedure given by Soliman et al.\(^{7}\) However, the reaction of 2,5-diamino-3,6-dibromoquinone (3b) (Scheme 2) with ethyl acetocetate, triethylamine in refluxing DMF resulted only in the isolation of starting material, the reaction was unsuccessful. However, a recently reported one-pot synthesis of 2,5,6-trimethyl-1H-indole-4,7-dione (7) from the photolytic reaction of 2-amino-5,6-dipyrrolo-1,4-benzoquinones. These are, (i) synthesis of terreusinone (Figure 1); for this we needed the reaction of 2,5-diamino-3,6-dibromoquinone (11) was prepared starting from 1,4-benzoquinone in quantitative yield following the procedure of Hegedus et al.\(^{10b}\) (Scheme 4). The 2,5-diamino-1,4-benzoquinone (1) was synthesized by hydrogenolysis of 11 with catalytic amounts of 5% palladium on charcoal\(^{11}\) at 45 psi in methanol at ambient temperature. Subsequent base hydrolysis with triethylamine in methanol–water (1:1) resulted in the formation of 1 in 82% yield. Compound 1 turned reddish-brown to black at 325–330 °C and did not melt till 360 °C.\(^{2}\) Product 1 was fully characterized by analysis of its spectral data. The \(^{1}\)H NMR\(^{12}\) spectrum of 1 showed two singlets for the four amino H-atoms at \(\delta = 7.05\) and 7.80 and the two equivalent vinyl H-atoms at \(\delta = 5.32\). The IR spectrum showed characteristic absorptions for the amino group at 3200 cm\(^{-1}\). The mass spectrum of 1 showed a molecular ion at \(m/z\) 138, consistent with the formula C\(_8\)H\(_{10}\)N\(_2\)O\(_2\). The IR, \(^{1}\)H NMR, and mass spectra are in complete agreement with its structure.

In conclusion, an efficient synthesis of 2,5-diamino-1,4-benzoquinone (1) has been developed with success using hydrogenolysis of 11 with catalytic amounts of palladium-on-charcoal. This procedure seems to be amenable to large-scale application.

Melting points were measured with a Fischer–Johns melting-point apparatus, and are not corrected. \(^{1}\)H NMR spectra were recorded with a Varian Unity 400 spectrometer (400 MHz) in DMSO-\(d_6\). Chemical shifts relative to TMS as internal standard are given as \(\delta\) values in ppm. IR spectra were taken with a PerkinElmer 1725FT spectrophotometer. EI-MS mass spectra were measured at 70 eV (EI). The abbreviations used are as follows: s, singlet; s, strong stretch; m, medium stretch; br, broad stretch. Compounds 1,4-benzoquinone (8)\(^{10a}\) and tetrabromo-1,4-hydroquinone (9)\(^{10b}\) were prepared according to the literature procedure.

Tetrabromo-1,4-benzoquinone (10)

This compound was prepared from tetrabromo-1,4-hydroquinone (9) according to the procedure described by Hegedus et al.\(^{10a}\)

\(\text{IR (KBr): 1690 (s, C=O), 1570 (m), 1550 (m), 700 cm}^{-1} (m).\)

\(\text{MS (EI): } m/z \% = 424 (20, [M + 2]^+), 422 (76), 345 (62), 316 (15), 183 (17), 130 (100), 79 (16).\)


2,5-Diamino-3,6-dibromo-1,4-benzoquinone (11)

This compound was prepared from p-bromoanil 10 according to Hegedus et al.10b

IR (KBr): 3390 (s, N-H), 3300 (s, N–H) 3240 (s, N–H) 1590 cm–1 (s, C=O).

1H NMR (400 MHz, DMSO-d6): δ = 7.82 (s, 2 H), 8.25 (s, 2 H).

MS (EI): m/z (%) = 296 (75, [M + 2]+), 217 (47), 187 (6), 148 (9), 120 (10), 80 (21), 68 (100), 52 (17), 40 (47).


2,5-Diamino-1,4-benzoquinone (1)

To a solution of 2,5-diamino-3,6-dibromoquinone (11; 20 g, 67.6 mmol) in MeOH (400 mL) in a Büchi hydrogenation glass vessel (1 L), was added 5% Pd/C (2 g, w/w 10%), and the suspension was hydrogenated at 45 Psi for 6 h at r.t. The mixture was filtered, the filtrate (pH 2 to 3) was treated with Et3N (15.4 g, 152 mmol) and H2O (400 mL) at 10 °C and the mixture was stirred at r.t. (pH 10–12) for 4.5 h. The precipitate was collected by filtration, washed with H2O (2 × 50 mL), and dried in vacuum to give analytical pure 1 as a bright reddish-brown crystalline solid; yield: 7.6 g (82%); mp >360 °C (Lit.4,5 mp 325–330 °C).

IR (KBr): 3360 (s, N–H), 3200 (s, N–H), 1530 cm–1 (s, C=O).

1H NMR (400 MHz, DMSO-d6): δ = 5.32 (s, 2 H), 7.04 (br s, 2 H), 7.80 (br s, 2 H).

MS (EI): m/z (%) = 139 (86, [M + 1]+), 111 (16), 70 (23), 41 (100).


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