A Novel High-Yield Synthesis of Substituted Isoindolequinones

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Received September 8, 1997[⊗]

The high-yield, general, one-pot synthesis of substituted isoindolequinones, a group of important radiosensitizers which sensitize hypoxic cells to the lethal effect of radiation in cancer radiotherapy, is described. Primary amines react with 2,3-bis[2-(trimethylsilyl)ethynyl]-5,6-dimethylhydroquinone (**2**) in methanol at room temperature under an inert atmosphere to give substituted isoindolequinones 2-alkyl-1,3,5,6-tetramethylisoindole-4,7-quinone (**4**) in almost quantitative yields. Moderate yields of **4** are also obtained using 2,3-diethynyl-5,6-dimethylhydroquinone (**3**) and amines as reactant and solvent under the similar conditions. Tris(2-aminoethyl)amine (TREN) reacts with **2** in MeOH/THF on reflux to produce the isoindolequinone derivative of TREN. Water with **2** on reflux in MeOH forms an isobenzofuranquinone. This indicates that the formation of similar heterocycles from small molecules (e.g., Group VA and VIA hydrides) and **2** is likely. Readily synthesizable starting materials, ease of chromatographic isolation of the product, reaction generality, use of no catalyst, and cost-effective environmentally benign solvents such as MeOH/EtOH make this novel reaction simple and convenient.

Introduction

Isoindolequinones have been shown to have useful radiosensitization properties, in that they selectively sensitize hypoxic cells in some tumors to the lethal effect of radiation.[1,2] Isoindolequinones were first synthesized by the treatment of rhodium heterocycles, prepared from diketodiynes and Wilkinson's catalyst, with nitrosobenzene[3] in very low yield (5%). Cycloadditions of oxazolium 5-oxides to 1,4-benzoquinones also give isoindole derivatives in moderate yields.[4,5] The first reported naturally occurring isoindolequinone, 2,5-dimethyl-6-methoxyisoindole-4,7-quinone,[6] isolated from the sponge *Reniera*, has been synthesized in moderate yields from a pyrrole derivative[7] and by the cycloaddition of an ylide to a quinone.[8] Zinc-induced intramolecular cyclizations of bis(bromoacetyl)heteroaromatic compounds also give isoindolequinones in good yields.[9]

Results and Discussion

We report a convenient, novel, high-yield synthesis of substituted isoindolequinones from a diethynylhydroquinone and primary amines by a tandem reaction. The combination of 2,3-bis[2-(trimethylsilyl)ethynyl]-5,6-dimethylhydroquinone (**2**) and 1 molar equiv of a primary amine in methanol under an inert atmosphere results in the formation of isoindolequinones **4** in almost quantitative yields.

The palladium−copper-catalyzed coupling of 2,3-diiodo-5,6-dimethylhydroquinone[10] (**1**) with (trimethylsilyl)-acetylene (TMSA) gives precursor **2** in 50% yield. Desilylation of **2** by potassium fluoride in methanol at rt gives 2,3-diethynyl-5,6-dimethylhydroquinone (**3**) in 52% yield. We first encountered compound **4** (R^2 = isopropyl) as a side product in a standard palladium−copper-catalyzed coupling reaction to form an ene−yne cyclic compound from **3** as one of the starting materials and diisopropylamine as solvent. The reaction conditions initially used in exploring the transformation of **3** into **4** involved the use of amines as reactants and solvents and the presence and absence of $Pd(PhCN)_2Cl_2$ and PPh_3 to check the role of catalyst. The production of isoindolequinones proceeds with or without the catalyst, but with increased yields (by about 10−20%) when the catalyst is present. The trimethylsilyl derivative of **3**, 2,3-bis[2-(trimethylsilyl)ethynyl]-5,6-dimethylhydroquinone (**2**), undergoes reaction with primary amines using the amine as both reactant and solvent to produce the same products as **3** under similar conditions and with approximately the same yields (37−78%). Surprisingly, a 32% yield of the isopropyl derivative of **4** (R^2 = *i*-Pr) has been isolated on reaction of **3** with the secondary amine *i*-Pr_2NH on reflux, using *i*-Pr_2NH as solvent, but the formation of **4** is not observed at rt. The formation of **4** (R^2 = *i*-Pr) from **2** and *i*-Pr_2NH is not observed at rt or at reflux with MeOH as solvent. Compound **4** (R^2 = *i*-Pr) has been structurally characterized by pulsed field gradient (PFG) heteronuclear multiple bond correlation (HMBC) and heteronuclear multiple quantum correlation (HMQC) NMR experiments.[11] Neither compound **2** nor **3** reacts with triethylamine. The production of **4** is not observed in aprotic solvents such as tetrahydrofuran or toluene with as much as 5 equiv of a primary amine, but the reaction does proceed if methanol or ethanol is used as

⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1997.

(1) Myers, J. A. U.S. Patent 4 494 547, 1985.
(2) *Radiat. Sensitizers: Their use Clin. Manage. Cancer 1980* (Conference Proceedings); Brady, L. W., Ed.; Masson USA: New York, 1980; pp 497−501.
(3) (a) Müller, E.; Winter, W. *Liebigs Ann. Chem.* **1974**, 1876. (b) Müller, E.; Luppold, E.; Winter, W. *Chem. Ber.* **1975**, *108*, 237. (c) Hambrecht, J.; Straub H.; Müller E. *Tetrahedron Lett.* **1976**, *21*, 1789. (d) Müller, V. E.; Dilger, W. *Chem.-Ztg.* **1973**, *97*(7), 388.
(4) Matsukubo, H.; Kato H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3333.
(5) Myers, J. A.; Moore, L. D. Jr.; Whitter, W. L.; Council, S. L.; Waldo, R. M.; Lanier, J. L.; Omoji, B. U. *J. Org. Chem.* **1980**, *45*, 1202.
(6) Thomson, R. H. *Naturally Occuring Quinones III: recent advances*; Chapman and Hall: New York, 1987; pp 657−658.
(7) Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265.
(8) Parker, K. A.; Cohen, I. D.; Padwa, A.; Dent, W. *Tetrahedron Lett.* **1984**, *25*, 4917.
(9) Ghera, E.; Gaoni, Y.; Perry, D. H. *J. Chem. Soc., Chem. Commun.* **1974**, *24*, 1034.
(10) Nicolaou, K. C.; Liu, A.; Zeng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279−9282.
(11) Rinaldi, P. L.; Ray, D. G.; Litman, V. E.; Keifer, P. A. *Polymer Int.* **1995**, *36*, 177.

S0022-3263(97)01671-X CCC: $14.00

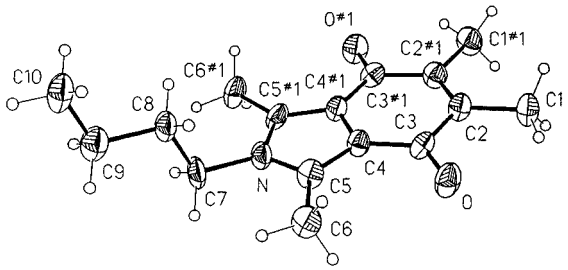
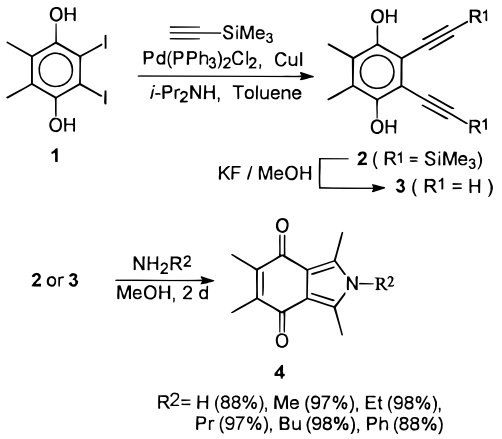
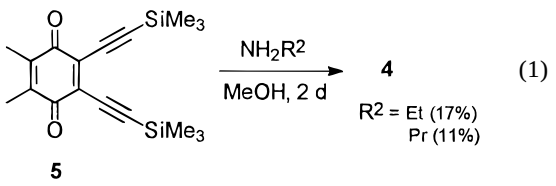


Figure 1. Thermal ellipsoid plot of **4** (R^2 = Bu).

Scheme 1

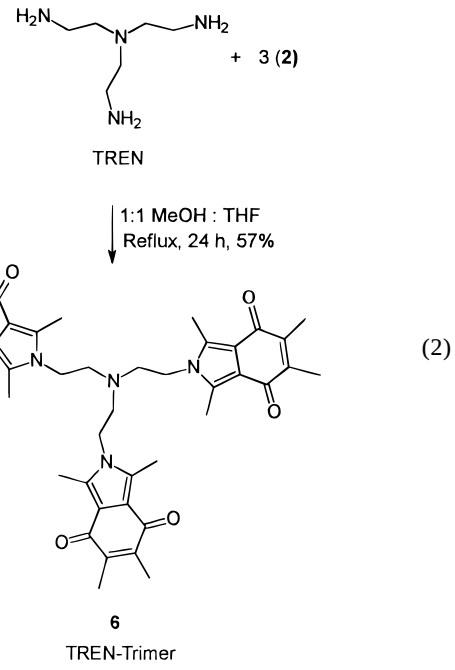


cosolvent. The quinonoid form of **2** (**5**) reacts with ethyl- and propylamines in methanol to give isoindolequinones **4** in 17% and 11% yields, respectively (eq 1). It is probable that the quinonoid precursor is reduced to the hydroquinone form (**2**) in presence of amine which then undergoes further reaction.



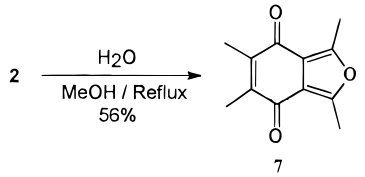
(1)

The combination of **2** with 1.5−1.7 molar equiv of methyl-, ethyl-, propyl-, or butylamine in degassed methanol gives **4** in greater than 97% yield when the mixtures are stirred at rt for 2 days (Scheme 1). Pure yellow products were isolated by flash column chromatography eluting with 3% ethyl acetate in petroleum ether. The combination of ammonium hydroxide with **2** in MeOH gives 1,3,5,6-tetramethylisoindole-4,7-quinone, **4** (R^2 = H), in 88% yield. The combination of the desilylated derivative **3** and propylamine in methanol gives a 48% yield of **4** (R^2 = Pr) at room temperature. This lower yield may be due to the poor solubility of **3** relative to that of **2** in MeOH. Aniline does not react with **2** at rt in methanol, but when the mixture is heated at 80 °C for 12 h, **4** (R^2 = Ph) is isolated in 88% yield. Melamine, adenine, guanine, and cytosine give no reaction when combined with **2** in methanol or in methanol/H_2O/DMSO mixtures at rt or reflux. This is presumably due to the very low nucleophilicity of these bases. The combination of **2** with tris(2-aminoethyl)amine, TREN, in a 1:3 ratio in 1:1 MeOH:THF at reflux gives **6** in 57% yield (eq 2). When the R^1 group in **2** is a phenyl ring, no reaction with amines is observed.



(2)

The presence of a small amount of water (0.02% in commercially available methanol) does not appear to affect isoindolequinone formation. However, the combination of **2** with propylamine in 10% water−ethanol gives a 73% yield of **4** (R^2 = Et). Without water present, a 98% yield is obtained. The combination of **2** with water in methanol at reflux affords the isobenzofuranquinone **6** (eq 3) in 56% yield.

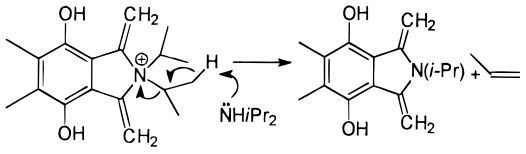


(3)

All products were characterized by ^1H and ^{13}C NMR, infrared, and mass spectroscopies and elemental analysis (C and H). The structure of the butyl derivative **4** (R^2 = Bu) has been confirmed by X-ray crystallography (Figure 1).

An important observation, when speculating on the mechanism of these reactions, is that the best yields are obtained when protic solvents are employed. The production of isoindolequinones **4** from **3** and primary amines is believed to be the result of anionic tandem reactions (Scheme 2), comprising base-catalyzed tautomerizations, Michael reactions, and proton transfers. The series seems to be initiated by base-catalyzed tautomerization (steps i and ii) of the hydroquinone (**3**) to ketylallene intermediate **7**. Michael addition by amine on **7** (step iii) and proton transfer (step iv) from solvents or amine gives **8**. Intermolecular Michael addition on the remaining allene (v) followed by proton transfer gives (vi) **9**. Two steps of base-catalyzed tautomerization (vi) ultimately yield isoindolequinone **4**. In the case of diisopropylamine (eq 4) it is assumed that the initial product is a diisopropylammonium ion which undergoes β elimination with excess amine to give propylene and the monoisopropylisoindole system **4a** (R^2 = *i*-Pr).

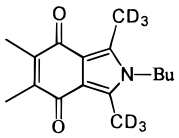
(12) Hartley, F. R. *Organomet. Chem. Rev. A* **1970**, *6*, 119.



(4)

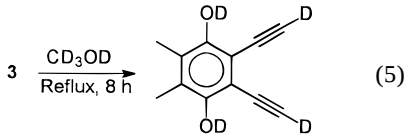
10 (R^2 = *i*-Pr)

When the reaction of **2** and excess butylamine was carried out in CD_3OD, 80% deuterium incorporation in the methyl groups adjacent to the nitrogen was observed by ^1H NMR and **4** (D_6, R^2 = Bu) was obtained. When **3**



4 (D_6, R^2 = Bu)

was refluxed for 8 h in CD_3OD, the quantitative conversion to **11** was observed (eq 5). This is consistent with the reversible formation of ketoallenes such as **7** from **3** as in Scheme 2.



(5)

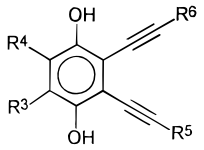
11

Conclusions

Readily synthesizable starting materials, one-pot conversions, high-yields, and ease of chromatographic isolation of products make this isoindolequinone synthesis simple and convenient. In addition the reaction requires no catalyst and uses environmentally benign solvents (MeOH or EtOH). This reaction can be expected to have potential use in the high-yield synthesis of substituted isoindolequinone systems. We are in the process of further investigation of this reaction and its extension to other amines and substrate systems. We are also exploring the synthesis and reaction chemistry of variously substituted 2-(2-(R_5)ethynyl)-3-(2-(R_6)ethynyl)-5-(R_3)-6-(R_4)hydroquinones **12** with amines, water, H_2S, and other small molecules.

Experimental Section

Materials. All chemicals were reagent grade materials. The compounds 2,3-diiodo-5,6-dimethylhydroquinone (**1**)[10] and bis(benzonitrile)palladium dichloride[12] were prepared by literature procedures. Methylamine in methanol (2 M), ethylamine in ethanol (2 M), butylamine, deuterated methanol (CD_3OD), potassium fluoride, copper iodide, barium oxide, and



12

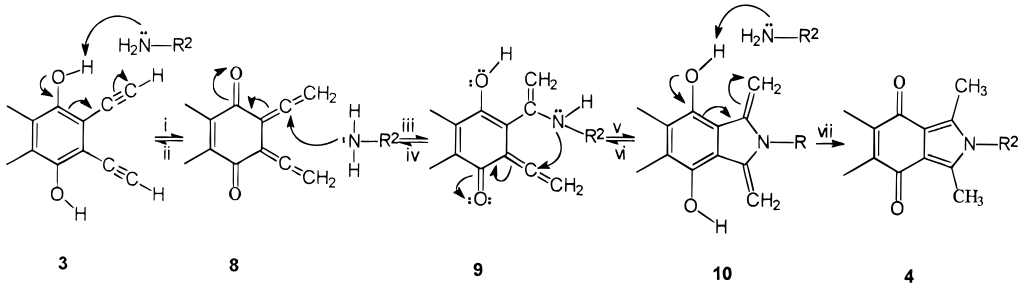
(trimethylsilyl)acetylene (Aldrich), propylamine (Lancaster), triphenylphosphine (Janssen Chimica), aniline, methanol, ethanol, carbon tetrachloride, acetonitrile, magnesium sulfate (Fisher), and deuterated chloroform (Cambridge Isotope Laboratory) were used as received. Tetrahydrofuran and toluene (Fisher) were distilled from sodium and benzophenone under nitrogen. Isopropylamine (Lancaster) and diisopropylamine (Janssen Chimica) were distilled from BaO and KOH, respectively.

General Techniques. Field desorption mass spectra (FDMS) were obtained by Dr. Robert Lattimer at BF Goodrich in Brecksville, OH. High-resolution mass spectra (HRMS) were obtained by the Nebraska Center for Mass Spectrometry. Unless specified otherwise, all reactions were conducted under argon by standard Schlenk techniques. The amines and methanol used in reactions were degassed by three freeze−pump−thaw cycles. Reaction temperatures were monitored externally. All reactions were monitored by thin-layer chromatography (TLC) on E. Merck silica gel plates (60F-254) using UV light. Flash column chromatography was performed on silica gel (Baker: 40 μm). Elemental analyses were performed by Midwest Microlab in Indianapolis, IN, and Schwarzkopf Microanalytical Laboratory, NY.

2,3-Bis[2-(trimethylsilyl)ethynyl]-5,6-dimethylhydroquinone (2). To a solution of 2,3-diiodo 5,6-dimethylhydroquinone[10] (**1**, 3.60 g, 9.23 mmol), $Pd^{II}(PhCN)_2Cl_2$ (176 mg, 0.46 mmol), PPh_3 (278 mg, 1.06 mmol), and CuI (297 mg, 1.56 mmol) in toluene (110 mL) were added diisopropylamine (2.50 mL, 18.5 mmol), and (trimethylsilyl)acetylene (4.00 mL, 28.6 mmol). After being stirred at room temperature for a day, the reaction mixture was opened to air, filtered, and concentrated in vacuo. Flash column chromatography of the crude solid with 7% ethyl acetate in petroleum ether gave **2** as a yellow solid: yield, 1.53 g (50.2%); mp 79−80 °C; ^1H NMR ($CDCl_3$) δ 0.29 (s, 18 H, 2 $SiMe_3$), 2.18 (s, 6 H, 2 CH_3), 5.63 (s, 2 H, 2 OH); ^{13}C NMR ($CDCl_3$) δ 0.01,12.42, 98.04, 104.68, 106.81, 125.67, 149.02; IR (Nujol solution) ν 3483 (s, OH), 2957 (s, CH_3 on benzene ring), 2141 (s, C≡C) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 236 (4.13), 262 (s, 3.53), 278 (3.71), 288 (3.76), 348 (3.45), 358 (3.46) nm; HRMS (EI) calcd for $C_{18}H_{26}O_2Si_2$ 330.1471, found 330.1472 (err 0.43 ppm).

2,3-Diethynyl-5,6-dimethylhydroquinone (3). A solution of **2** (375 mg, 1.14 mmol), KF (198 mg, 3.40 mmol), MeOH (35 mL), and H_2O (2.9 mL) was stirred in air at room temperature for 1 h. The reaction was monitored by TLC every 10 min after the first half hour had elapsed. When the starting material spot on the TLC disappeared (after 20 min), the mixture was quenched with water (20 mL). Otherwise the product was found to polymerize. The reaction mixture was then extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were washed thoroughly with H_2O (3 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography of the crude solid with 7% ethyl acetate in

Scheme 2



petroleum ether gave the title compound as a creamy white solid: yield, 111 mg (52%); mp, gets darker after 133 °C and melts between 151 and 152 °C; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 6 H, 2 CH_3), 3.65 (s, 2 H, 2 alkynyl H), 5.59 (s, 2 OH); ^{13}C NMR ($CDCl_3$) δ 12.70, 86.88, 95.70, 105.95, 126.70, 149.80; IR (CCl_4) ν 2099 (w, C≡C), 2931 (w, CH_3 on benzene ring), 3308 (s, C≡CH), 3533 (m, OH) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 346 (4.05), 272 (4.24), 264 (4.22), 224 (4.68) nm; FDMS found for $C_{12}H_{10}O_2$ 186 (M^+). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.36; H, 5.37. Found: C, 77.20; H, 5.34.

General Procedure A: Synthesis of Isoindolequinones 4 from 2,3-Bis[(trimethylsilyl)ethynyl]-5,6-dimethylhydroquinone (2) in Methanol. All the compounds except the isopropyl derivative have been synthesized using this procedure. To a colorless solution of **2** in methanol was added an amine via syringe (1.2−1.4 molar equiv) under argon, and the solution was stirred at room temperature. The solution immediately assumed an orange yellow color that turned into bright yellow within half an hour and was stirred for 2 days at room temperature. After the reaction vessel was opened to air, the volatiles were removed in vacuo. Flash column chromatography of the residual materials gave pure yellow isoindolequinones in 97−98% yield in most cases.

2-Propyl-1,3,5,6-tetramethylisoindole-4,7-quinone, 4 (R^2 = Pr). Following procedure A, MeOH (0.80 mL) and *n*-propylamine (0.02 mL, 0.24 mmol) were added to **2** (46.2 mg, 0.14 mmol). Column chromatography with 3% ethyl acetate in petroleum ether gave the title compound as a yellow solid: yield, 33.3 mg (97%); mp 163−164 °C; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 6 H, 2 CH_3), 2.57 (s, 6 H, 2 CH_3), 0.97 (t, 3 H, J = 7.0 Hz, CH_3), 1.69 (tq, 2 H, J = 7.4 Hz, CH_2), 3.79 (t, 2 H, J = 7.4 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 11.27, 12.66, 14.16, 23.59, 44.80, 116.76, 135.34, 144.06, 183.17; IR (CCl_4) ν 1641 (s, C═O), 2927 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 208 (4.42), 222 (4.46), 264 (4.33), 396 (3.88, br) nm; FDMS found for $C_{15}H_{19}O_2N$ 245 (M^+). Anal. Calcd for $C_{15}H_{19}O_2N$: C, 73.46; H, 7.75; N, 5.71. Found: C, 73.20; H, 7.61; N, 5.70.

2-Butyl-1,3,5,6-tetramethylisoindole-4,7-quinone, 4 (R^2 = Bu). Procedure A was followed using **2** (49.50 mg, 0.15 mmol), butylamine (0.02 mL), and MeOH (2 mL). Column chromatography (3% ethyl acetate in petroleum ether) gave the butyl derivative as a yellow solid: yield, 38.1 mg (98%); mp 172 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 6 H, 2 CH_3), 2.56 (s, 6 H, 2 CH_3), 0.97 (t, 3 H, J = 7.2 Hz, CH_3), 1.38 (m, 2 H, CH_2), 1.6 (m, 2 H, CH_2), 3.78 (t, 2 H, J = 7.4 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 11.22, 12.65, 13.79, 20.14, 32.36, 43.12, 116.74, 135.27, 144.02, 183.13; IR (CCl_4) ν 1642 (s, C═O), 2928 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 202 (4.22), 222 (4.19), 266 (4.01), 396 (3.52, br) nm; FDMS found for $C_{16}H_{21}O_2N$ 259 (M^+). Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.09; H, 8.16; N, 5.40. Found: C, 73.81; H, 8.46; N, 5.33.

2-Phenyl-1,3,5,6-tetramethylisoindole-4,7-quinone, 4 (R^2 = Ph). This compound was prepared (procedure A) from **2** (49.5 mg, 0.15 mmol), aniline (0.02 mL), and MeOH (2 mL). The residue, after column chromatography with 3% ethyl acetate in petroleum ether, gave the phenyl derivative (yellow solid): yield, 36.8 mg (88%); mp, melts with blackening between 239 and 241 °C; ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 6 H, 2 CH_3), 2.34 (s, 6 H, 2 CH_3), 7.21, 7.55, (two sets of m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 12.07, 12.74, 116.88, 128.19, 129.78, 130.13, 136.06, 136.46, 144.35, 183.28; IR (CCl_4) ν 1643 (m, C═O), 2927 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 206 (4.21), 226 (4.16), 258 (4.02), 394 (3.52, br) nm; HRMS (EI) calcd for $C_{18}H_{17}O_2N$ 279.1259, found 279.1257 (err −0.55 ppm).

2-Methyl-1,3,5,6-tetramethylisoindole-4,7-quinone, 4 (R^2 = Me). A 2 M solution of $MeNH_2$ in MeOH was used as received. The 2 M solution of $MeNH_2$ in MeOH (9.0 mL, 18 mmol) was added via syringe to **2** (59.4 mg, 0.18 mmol) under argon and procedure A was followed. Column chromatography of the residual solid with 4% ethyl acetate in petroleum ether gave the product, a yellow solid, in 97% yield (37.9 mg): mp 228−229 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 6 H, 2 CH_3), 2.56 (s, 6 H, 2 CH_3), 3.43 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 11.25, 12.65, 29.82, 116.58, 135.65, 144.02, 183.09; IR (CCl_4) ν 1643 (m, C═O), 2926 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 202 (3.88), 222 (3.82), 262 (3.70), 396 (3.21, br) nm; FDMS found for $C_{13}H_{15}O_2N$ 217 (M^+). Anal. Calcd for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.95; N, 6.44. Found: C, 71.60; H, 6.90; N, 6.24.

2-Ethyl-1,3,5,6-tetramethylisoindole-4,7-quinone, 4 (R^2 = Et). A 2 M solution of $EtNH_2$ in EtOH was used as received. Using procedure A, the 2 M solution of $EtNH_2$ in EtOH (9.0 mL, 18 mmol) was added to **2** (59.4 mg, 0.18 mmol) via syringe. Column chromatography (3% ethyl acetate in petroleum ether) gave the ethyl derivative as a yellow solid in 98% yield (40.8 mg): mp 166 °C; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 6 H, 2 CH_3), 2.58 (s, 6 H, 2 CH_3), 3.85 (q, 2 H, J = 7.2 Hz, CH_2), 1.30 (t, 3 H, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 11.01, 12.66, 15.38, 38.04, 116.83, 134.96, 144.05, 183.16; IR (CCl_4) ν 1640 (s, C═O), 2928 (w, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 200 (3.81), 222 (3.70), 264 (3.57), 398 (3.02, br) nm; HRMS (EI) calcd for $C_{14}H_{17}O_2N$ 231.1259, found 231.1259 (err 0.02 ppm).

1,3,5,6-Tetramethylisoindole-4,7-quinone, 4 (R^2 = H). General procedure A was followed using **2** (39.6 mg, 0.12 mmol) and 2 mL of MeOH saturated with ammonia. The mixture was stirred at room temperature for 12 h. Column chromatography (20% ethyl acetate in petroleum ether) gave the title compound as a yellow solid: yield, 21.4 mg (88%); mp, turns black after 290 °C and becomes totally black until 360 °C without melting; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3 H, CH_3), 2.55 (s, 3 H, CH_3) 8.15 (s, H, br); ^{13}C NMR (in DMSO, referenced at δ 39.51) δ 12.01, 12.27, 115.95, 134.08, 143.29, 181.82; IR (CCl_4) ν_{max} 1641 (m, C═O), 2927 (m, CH_3), 3244 (m, N−H) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 208 (4.06), 216 (4.04), 260 (3.95), 394 (3.47, br) nm; HRMS (FAB) calcd for $C_{12}H_{14}O_2N$ (M + H) 204.1025, found 204.1026 (err −0.7 ppm).

Compound 6. To a solution of **2** (201 mg, 0.61 mmol) in MeOH:THF (20 mL:20 mL) was added tris(2-aminoethyl)-amine or TREN (0.03 mL, 0.2 mmol, d = 0.97) via syringe. The mixture was stirred at room temperature for 12 h and refluxed for 24 h. After the reaction mixture was opened to air, the volatiles were removed in vacuo. Flash column chromatography (with 55% ethyl acetate in petroleum ether) gave the TREN derivative of **4**, a yellow solid, in 57% yield (81.5 mg): mp, melts with decomposition within 270−278 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 18 H, 6 CH_3), 2.55 (s, 18 H, 6 CH_3), 2.79 (t, 6 H, J = 7.1 Hz, 3 CH_2), 3.77 (t, 6 H, J = 7.1 Hz 3 CH_2); ^{13}C NMR ($CDCl_3$) δ 11.27, 12.66, 41.69, 55.05, 117.14, 134.36, 144.25, 182.92; IR (CCl_4) ν 1632 (m, C═O), 2928 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 202 (4.65), 224 (4.61), 260 (4.50), 394 (4.10) nm; HRMS (FAB) calcd for $C_{42}H_{49}O_6N_4$ (M+H) 705.3653, found 705.3661 (err −1.3 ppm).

1,3,5,6-Tetramethylisobenzofuran-4,7-quinone (7). To a solution of **2** (201 mg, 0.61 mmol) in MeOH was added H_2O (5 mL), and the mixture was refluxed for a day. Removal of the solvents and column chromatography of the solid residue with 1% ethyl acetate in petroleum ether gave the title compound as a yellow product in 56% yield (69.6 mg): mp 145−147 °C; ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 6 H, 2 CH_3), 2.60 (s, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 12.80, 13.43, 116.75, 145.91, 156.23, 182.19; IR (CCl_4) ν 1620 (s, C═O), 2928 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 214 (4.00), 248 (4.04), 298 (3.51), 364 (3.46) nm; FDMS found for $C_{12}H_{12}O_3$ 204 (M^+). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.61; H, 6.01.

General Procedure B: Synthesis of Isoindolequinones 4 from Amine as Solvent and Reactant and 2 or 2,3-Diethyny1-5,6-dimethylhydroquinone (3). A series of reactions were carried out using **2** or **3** and excess amines as reactants. In some of the cases a palladium catalyst was used. In a typical reaction in the presence of catalyst, **2** or **3** was combined with 5% bis(benzonitrile)palladium dichloride (Pd^{II}-$(PhCN)_2Cl_2$), 12% triphenylphosphine (PPh_3), and excess amine and stirred at room temperature for a day, followed by refluxing for 8−12 h (depending upon the requirement). Similar reactions without catalyst were carried out using amines as received. The yields of the products in these cases were moderate to good (40−78%). This procedure has been found to be exclusive for the synthesis of the isopropyl derivative of **4** from diisopropylamine.

2-Isopropyl-1,3,5,6-tetramethylisoindole-4,7-quinone, 4 (R^2 = *i*-Pr). To a mixture of **3** (50.2 mg, 0.27 mmol), $Pd(PhCN)_2Cl_2$ (4.00 mg, 0.01 mmol), and PPh_3 (10.4 mg, 0.04

mmol) was added isopropylamine (12 mL) and the solution was stirred overnight at room temperature. Column chromatography (3% ethyl acetate in petroleum ether) gave the product, a yellow solid, in 49% yield (32.5 mg): mp 162−163 °C; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, 6 H, J = 7.1 Hz, 2 CH_3), 2.05 (s, 6 H, 2 CH_3), 2.67 (s, 6 H, 2 CH_3), 4.52 (h, 1 H, J = 7.1 Hz, isopropyl); ^{13}C NMR ($CDCl_3$) δ 12.58, 12.79, 21.83, 47.72, 116.98, 135.58, 143.94, 183.03; IR (CCl_4) ν 1643 (s, C=O), 2930 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 202 (4.03), 224 (4.01), 264 (3.87), 398 (3.40, br) nm; FDMS found for $C_{15}H_{19}O_2N$ 245 (M^+). Anal. Calcd for $C_{15}H_{19}O_2N$: C, 73.46; H, 7.41; N, 5.71. Found: C, 73.50; H, 7.07; N, 5.42.

Deuteration Study. Reaction of Butylamine and 2 in CD_3OD, 4 (D_6, R^2 = Bu). An NMR tube was assembled with **2** (10.0 mg, 0.03 mmol), butylamine (0.01 mL), and 0.5 mL deuterated methanol (CD_3OD) in the drybox. The ^{1}H NMR spectrum was monitored at rt every half hour for the first 5 h and every 10 h after that. The peak at δ 2.04 (due to the methyls on the quinone ring) remained unchanged but the peak at δ 2.56 (corresponding to the methyls adjacent to the nitrogen) appeared as a small multiplet after 2 days. Integration showed 80% deuterated product containing D in the two methyls on the pyrrole ring distributed in the products of molecular weight (FDMS) 261 (1%), 262 (9%), 263 (28%), 264 (40%), 265 (22%).

Heating 3 in CD_3OD (11). Two NMR tubes were assembled having **3** (10 mg) in CD_3OD in the presence and absence of air at rt, and the ^{1}H NMR spectrum was monitored every half hour. The spectrum remained unchanged at rt but upon reflux for 8 h the alkyne hydrogens were completely exchanged with deuterium under both conditions.

Acknowledgment. We thank the National Institute of General Medicine, National Institutes of Health (Grant 1R15GM54294-01), and the National Science Foundation (DMR-9310642 and DMR-9617477) for financial support. We also thank Dr. Robert Lattimer of BF Goodrich for providing FDMS data and the Nebraska Center for Mass Spectrometry for HRMS data.

Supporting Information Available: HMQC and HMBC data for compound **4** (R^2 = *i*-Pr), and the X-ray crystal data for compound **4** (R^2 = Bu) (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971671R