

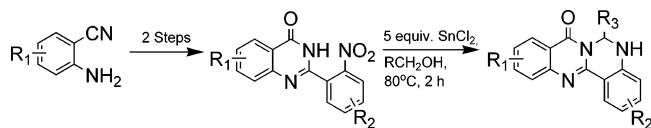
Auto-Redox Reaction: Tin(II) Chloride-Mediated One-Step Reductive Cyclization Leading to the Synthesis of Novel Biheterocyclic 5,6-Dihydro-quinazolino[4,3-*b*]quinazolin-8-ones with Three-Point Diversity[†]

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Received September 8, 2005



A tin(II) chloride-mediated short, efficient, and practical regioselective synthesis of biheterocyclic 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones with three-point diversity is reported. A one-step reductive transformation of 2-(2-nitrophenyl)-3*H*-quinazolin-4-one in various alcohols furnished the desired tetracyclic product in good yields with high purity.

Over the past decade, the synthesis of heterocycles has become the cornerstone of synthetic organic chemistry as a result of a wide variety of applications of these heterocycles in medicinal and pharmaceutical chemistry.¹ The exploration of heterocycles as privileged structures in drug discovery is, beyond doubt, one of the major areas in medicinal chemistry.² These privileged structures represent a class of molecules that act as ligands for various biological receptors with a high degree of binding affinity. Exploitation of these molecules should allow the medicinal chemist to rapidly discover new biologically active compounds across a broad range of therapeutic areas in a shorter time scale.³ In recent years, the emphasis of heterocyclic chemistry has relied on the synthesis of biheterocyclic structures that include conjugated tri- or tetracyclic molecules consisting of more than one privileged class of compounds.⁴

[†] CDRI Communication No. 6877.

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Among the nitrogen-containing heterocycles, substituted quinazolinones and quinazolines represent the medicinally and pharmaceutically important class of compounds⁵ because of their diverse range of biological activities such as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive agents.⁶ The quinazolin-4(3*H*)-ones ring system has traditionally been generated by the reaction of anthranilamides with aldehydes,⁷ ketones, or acid chlorides under acidic or basic conditions,⁸ by the condensation of imidates with anthranilic acid,⁹ and by aza-Wittig reactions of α -azido-substituted aromatic imides.¹⁰ The synthesis of quinazolinone derivatives has mainly been achieved by introducing the chlorine atom at the 4 position in the quinazolinone skeleton either by using POCl₃¹¹ or by using thionyl chloride,¹² followed by its substitution by various primary and secondary amines or by palladium-catalyzed intramolecular reductive *N*-heterocyclization.¹³

Although some of the methods provide useful strategies for the synthesis of these bicyclic compounds, they suffer major drawbacks, such as involving a multistep synthesis, producing low yields, and requiring expensive catalysts, and are, thus, less desirable commercially. Moreover, few methods exist in the literature for the one-step synthesis of quinazolin-4(3*H*)-ones, but they are not general in scope and require harsh conditions, such as a very high temperature¹⁴ and hazardous metal catalysts.¹⁵ While there are two reports¹⁶ available in the literature dealing with the synthesis of biheterocyclic quinazolinone-quinazolinone molecules, they involve multiple steps with

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low yields, strongly acidic conditions, the usage of commercially nonviable reagents, and poor regioselectivity that lead to the formation of both linearly and angularly fused compounds. However, these methods could achieve only 6-aryl-substituted molecules, and there has been no report regarding the synthesis of 6-alkyl-substituted quinazolino[4,3-*b*]quinazolin-8-one derivatives.

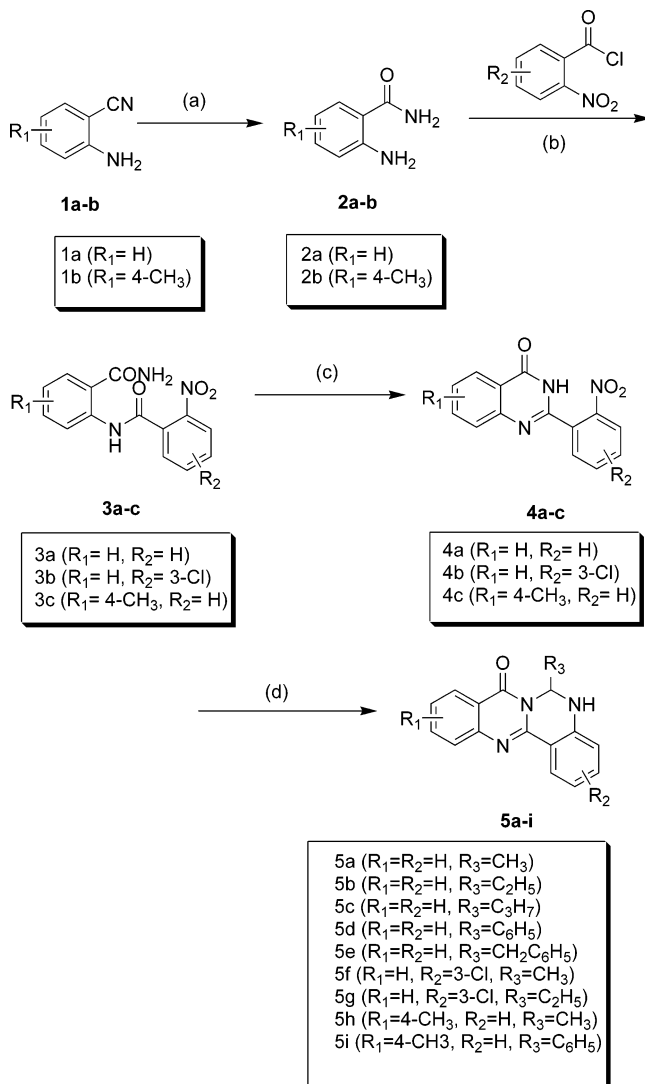
As per our ongoing efforts to synthesize privileged-class biheterocyclic molecules,¹⁷ we herein report a convenient and rapid one-step regioselective methodology for synthesizing biheterocyclic trisubstituted 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one derivatives from 2-(2-nitrophenyl)-3*H*-quinazolin-4-one in the presence of tin(II) chloride using a variety of alcohols.

The initial aim of our work was to synthesize 2-(2-aminophenyl)-3*H*-quinazolin-4-one derivatives. To accomplish this, it was first essential to synthesize 2-(2-nitrophenyl)-3*H*-quinazolin-4-one derivatives, followed by the reduction of the nitro group using tin(II) chloride, using ethanol as a solvent. Interestingly, the product obtained after the reduction was not the desired 2-amino derivative but rather an unusual dihydro-quinazolinoquinazolin-8-one derivative with a high yield and purity.

The strategy for the synthesis of 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one with three-point diversity has been depicted in Scheme 1. The synthetic methodology commenced with the synthesis of anthranilamide **2** by the oxidation of 2-amino benzonitrile, followed by its amidation using 2-nitro benzoyl chloride and triethylamine to give the uncyclized amide intermediate **3**. Subsequently, the 2-(2-nitrophenyl)-3*H*-quinazolin-4-one **4** was prepared by the oxidative ring closure of **3** under basic conditions, using potassium hydroxide and ethanol, in excellent yield and purity. Further, to obtain the amine functionality, attempts were made using the conventional procedure for the reduction of the nitro group using SnCl₂ and ethanol as a solvent, which furnished the final product in 90% yield and in high purity. The completion of the reaction was monitored by TLC at regular intervals, and the disappearance of the starting material was observed within 2 h. The unexpectedly high *R_f* value of the major product **5a** and a mass difference of 4 amu rather than the expected 30 amu led us to envisage the structure of the final product through one- and two-dimensional NMR spectroscopy.

The ¹H NMR spectrum of the final product **5a** showed a doublet accounting for three protons at 1.49 ppm, a multiplet accounting for one proton at 6.42 ppm, a broad signal at 4.61 ppm accounting for an exchangeable proton, and eight aromatic protons. Similarly, the ¹³C spectrum showed a methyl at 20.0 ppm and a methine carbon at 59.5 ppm, apart from the eight aromatic methines and six quaternary carbons, which further reinforced the formation of an unexpected product. In the heteronuclear single-quantum coherence (HSQC) spectrum, the multiplet at 6.4 ppm showed a correlation with the methine carbon at 56.0 ppm, which, in the heteronuclear multiple-bond correlation (HMBC) spectrum, provided a long-range two-bond correlation with the methyl carbon, followed by a three-bond correlation with three quaternary carbons, namely, the amide carbonyl at 160.1 ppm, the 2-position quaternary carbon at 146.7

SCHEME 1. Novel Strategy for the Synthesis of 5,6-Dihydro-quinazolino[4,3-*b*]quinazolin-8-one^a



^a Reagents and conditions: (a) 5 equiv of KOH, EtOH, reflux, 2 h, 80%; (b) 2 equiv of TEA, CHCl₃, rt, 2 h, 80–85%; (c) 10% aqueous KOH, EtOH, reflux, 10 min, 95%; (d) R₃CH₂OH, 5 equiv of SnCl₂·2H₂O, 80 °C, 1–2 h, 65–92% of **5a–i**.

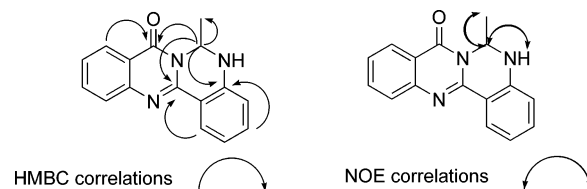
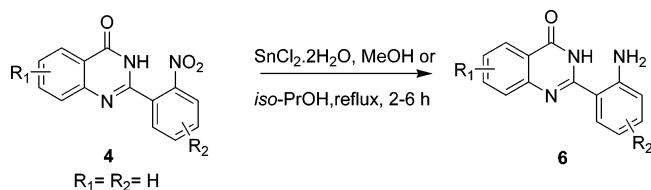


FIGURE 1. Selected HMBC and NOE correlations observed for **5a**. ppm, and the NH-substituted aromatic quaternary carbon at 143.7 ppm. The long-range heteronuclear proton carbon correlations established the structure of the final product as a novel 6-methyl-5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one **5a** formed after the insertion of the ethyl group between the primary aromatic amine and the secondary amide. The selected HMBC correlations observed for **5a** have been depicted in Figure 1. Further, the relative stereochemistry of the dihydro product was established by one-dimensional NOE, which indicated that the NH and the 6-position methine proton are cis in nature. Once

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SCHEME 2



the structure of the final product was established, the scope, limitations, and mechanism of the reaction were explored using a variety of alcohols, from low-boiling methanol to high-boiling phenethyl alcohol.

While the procedure worked nicely for many alcohols, such as *n*-propanol and *n*-butanol forming the *n*-propyl and *n*-butyl derivatives, respectively, the use of methanol and 2-propanol led to the synthesis of the undesired 2-(2-aminophenyl)-3*H*-quinazolin-4-one **6** (Scheme 2).

On the basis of the above observations, the authors propose the mechanism for the formation of **5** as the result of a redox reaction. It has been documented in the literature that the alcohols are prone to get oxidized to their corresponding aldehydes in the presence of tin(II) chloride and a base under an oxygen atmosphere.¹⁸ It was, therefore, envisioned that there might be a possibility of a reduction of the nitro group using tin(II) chloride along with the oxidation of the alcohols to the corresponding aldehydes, which in turn resulted in the formation of a Schiff base and ultimately led to the cyclization with the resulting diamine. The inability to form the dihydro product with methanol and 2-propanol could be explained on the basis of the formation of their corresponding oxidized products, which is formaldehyde in the case of the former and acetone in the case of the latter. It was thus anticipated that, under these reaction conditions, the formation of the Schiff base would not be feasible with both of the above-mentioned oxidized products.

Having thus obtained a plausible explanation for the indifferent behavior of methanol and 2-propanol, we turned our attention toward the mechanism of the formation of the cyclized product via a Schiff base intermediate. Interestingly, it was found that the mechanism for the formation of the amine and the subsequent conversion to the Schiff base was concerted. To establish this, a set of reactions was carried out under different temperatures and by varying the reaction times. It was observed that below 80 °C the reaction proceeded to form the stable undesired amine **6** instead of the dihydroquinazolinone **5**, irrespective of increasing the temperature afterward up to 100 °C or maintaining a longer reaction time of 6–8 h. This was further reconfirmed with the help of in situ NMR studies by mimicking the reaction conditions within the NMR tube so as to elucidate the reaction mechanism. The intermediate nitro **4**, 5 equiv of tin(II) chloride, and 10 equiv of ethanol were combined in ethanol-*d*₆, and the reaction was carried out at 70 °C. ¹H NMR spectra were recorded at regular intervals of 1.5 min for 3 h.

SCHEME 3

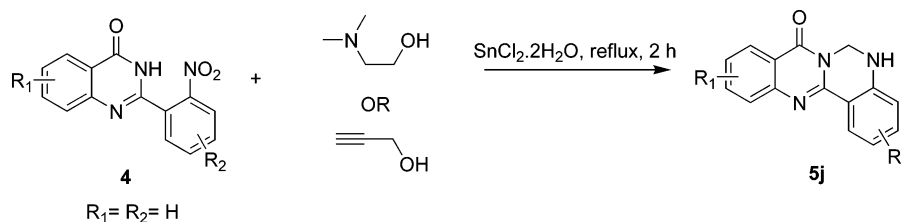


TABLE 1. Summary of the Conditions Used To Synthesize Tetracyclic Compounds **5a–j**

compd	R ₁	R ₂	R ₃	alcohol used	T (°C)	time (h)	yield
5a	H	H	–CH ₃	ethanol	80	2	85
5b	H	H	–CH ₂ CH ₃	<i>n</i> -propanol	90	2	72
5c	H	H	–CH ₂ CH ₂ CH ₃	<i>n</i> -butanol	90	2	64
5d	H	H	–C ₆ H ₅	benzyl alcohol	90	1	92
5e	H	H	–CH ₂ C ₆ H ₅	phenethyl alcohol	90	1	80
5f	H	3-Cl	–CH ₃	ethanol	80	2	78
5g	H	3-Cl	–CH ₂ CH ₃	propanol	80	2	68
5h	4-CH ₃	H	–CH ₃	ethanol	80	2	82
5i	4-CH ₃	H	–C ₆ H ₅	benzyl alcohol	90	1	73
5j	H	H	H	<i>N,N'</i> -dimethyl amino ethanol or propargyl alcohol	80	2	76

Throughout the whole reaction time, no marked changes were observed in the proton NMR spectra. TLC of the final mixture revealed the formation of the undesired amine **6**, reinstating the importance of the actual temperature being maintained during the reaction. Armed with these observations, we conclude that the optimal reaction conditions for the one-step synthesis of the novel 6-methyl-5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one **5** could be achieved by using 5 equiv of tin(II) chloride and by maintaining the temperature at 80 °C, bypassing the formation of the amine **6**.

Once the reaction conditions for the synthesis of the trisubstituted 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one **5** were optimized, a series of 10 compounds with three-point diversity were synthesized using five different alcohols as solvents. In addition to this, another interesting observation was identified while using two different alcohols for creating diversity, namely, dimethyl amino ethanol and propargyl alcohol. The product obtained in both cases was identified to be 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one **5j** instead of the expected dimethyl aminoethyl and propyne derivatives (Scheme 3). The product thus obtained was due to the elimination of the trimethylamine group in the former and ethyne in the latter.

During the preparation of the manuscript, a thorough search of any synthetic precedence for this type of synthetic transformation revealed only one very recent report stating the conversion of *o*-nitrobenzamides to bicyclic dihydroquinazolinones.¹⁹ This method, however, suffers from major drawbacks, such as the usage of an alcoholic HCl solution, a longer reaction time of 2 days, and the inability to achieve cyclization using high-boiling benzyl alcohol. It is noteworthy that, by using our present protocol, high-boiling phenethyl alcohol as well as benzyl alcohol furnished the expected products **5d**, **5e**, and **5h** in excellent yields and in a lesser reaction time of 1 h, whereas no product could be isolated following the reported method.¹⁹ A summary of the diversities used and the conditions for all the synthesized compounds are presented in Table 1.

In summary, the present methodology provides an entry for the convenient one-step synthesis of biheterocyclic 5,6-dihydro-

quinazolino[4,3-*b*]quinazolin-8-one derivatives with three-point diversity from the 2-(2-nitrophenyl)-3*H*-quinazolin-4-ones using a variety of alcohols, furnishing products with a high degree of yield and purity. All the compounds have been characterized using various one- and two-dimensional NMR spectroscopic techniques. The strategy can be useful for the synthesis of similar kinds of medicinally important conjugated heterocycles as well as in the generation of large libraries in fewer steps and in a shorter time scale, which is in contrast to the methods reported earlier.¹⁶

Experimental Section

General Considerations. See Supporting Information.

General Procedure for the Synthesis of 2-Amino Benzamide (2a). 2-Amino benzonitrile (**1a**, 1.04 g, 8.50 mmol) and potassium hydroxide (2.40 g, 42.5 mmol) were dissolved in hot ethanol (25 mL), and the reaction mixture was refluxed for 2 h. The resulting yellowish-brown solution was allowed to cool to room temperature, and the ethanol was removed in vacuo. The resulting brown solid was washed with water, a saturated solution of NaHCO₃, and brine and extracted with ethyl acetate (50 mL × 3). The organic layer was evaporated in vacuo, and the analytically pure product was obtained by recrystallization from ethanol as a white solid. **2a**: 0.96 g (80% yield); mp 112–114 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 6.45 (t, *J* = 7.8 Hz, 1H, ArH), 6.55 (br s, 2H, ArNH), 6.65 (d, *J* = 8.4 Hz, 1H, ArH), 7.05 [br s(o), 1H, –CONH], 7.11 [t(o), *J* = 8.1 Hz, 1H, ArH], 7.51 (d, *J* = 8.1 Hz, 1H, ArH), 7.90 (br s, 1H, –CONH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 113.7, 114.4, 116.4, 117.2, 128.8, 131.9, 150.2, 171.3. MS (FAB, *m/z*) 137 (M⁺ + 1). Anal. Calcd for C₇H₈N₂O: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.63; H, 5.94; N, 20.66.

N-[2-(Aminocarbonyl)phenyl]-2-nitrobenzamide (3a). 2-Nitrobenzoic acid (1.02 g, 6.1 mmol) and thionyl chloride (8 mL) were combined, and the reaction mixture was refluxed for 2 h at 80 °C. The solution was allowed to cool at room temperature, followed by the evaporation of the thionyl chloride in vacuo. The resulting wine-red solution was added dropwise to a solution of anthranilamide (**2a**; 1.04 g, 8.5 mmol) and triethylamine (3.1 mL, 17 mmol) in chloroform (25 mL) and stirred at room temperature for 2 h. The precipitated solid was filtered and washed with ethanol to obtain compound **3a**. The analytically pure sample was obtained by recrystallization from methanol as a white colored solid. **3a**: 2.2 g (86% yield); mp 195–197 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 7.22 (t, *J* = 8.4 Hz, 1H, ArH), 7.57 (t, *J* = 8.1 Hz, 1H, ArH), 7.75–7.90 (m, 5H, ArH and –CONH), 8.10 (d, *J* = 8.7 Hz, 1H, ArH), 8.34 (br s, 1H, –CONH), 8.46 (br d, *J* = 8.4 Hz, 1H, ArH), 12.49 (s, 1H, ArNH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 120.1, 120.4, 123.4, 124.6, 128.3, 128.7, 131.6, 132.0, 132.4, 134.0, 139.1, 147.1, 163.3, 170.6. MS (FAB, *m/z*) 286. Anal. Calcd for C₁₄H₁₁N₃O₄: C, 58.95; H, 3.89; N, 14.73. Found: C, 59.12; H, 3.98; N, 14.58.

2-(2-Nitrophenyl)-3*H*-quinazolin-4-one (4a). A mixture of benzamide (**3a**; 2.2 g, 7.0 mmol) in 10% aqueous KOH (50 mL) and EtOH (25 mL) was heated to reflux for 10 min. Ethanol was

removed in vacuo, and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The organic layer was washed with a saturated solution of NaHCO₃ and brine and dried over Na₂SO₄. The concentration of the organic layer in vacuo was followed by silica gel column chromatographic purification of the residue using hexanes–ethyl acetate as an eluant that gave pure **4a** as a light brown solid. **4a**: 1.8 g (95%); mp 210–212 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 7.57 (t, *J* = 7.5 Hz, 1H, ArH), 7.65 (d, *J* = 8.4, 1H, ArH), 7.80–7.94 (m, 4H, ArH), 8.19 (t, *J* = 8.1 Hz, 1H, ArH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 121.2, 124.6, 125.9, 127.1, 127.3, 129.2, 131.5, 131.6, 134.0, 134.7, 147.5, 148.5, 151.7, 161.6; MS (FAB, *m/z*) 268 (M⁺ + 1). Anal. Calcd for C₁₄H₉N₃O₃: C, 62.92; H, 3.39; N, 15.72. Found: C, 62.78; H, 3.56; N, 15.97.

6-Methyl-5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one (5a). A solution of **4a** (200 mg, 0.75 mmol) and SnCl₂·2H₂O (850 mg, 3.75 mmol) was dissolved in ethanol and refluxed at 80 °C for 2 h. The reaction mixture was concentrated in vacuo and diluted in ethyl acetate (10 mL). The organic layer was washed with saturated NaHCO₃ and a brine solution and dried over Na₂SO₄. The organic layer was evaporated under reduced pressure, and the residue was purified by column chromatography (5% EtOAc in hexane) to provide **5a** as a light yellow solid. **5a**: 170 mg (85% yield); mp 132–133 °C; ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (d, *J* = 5.4 Hz, 3H, –CH₃), 4.61 (br s, 1H, –NH), 6.42 (m, 1H, –CH), 6.77 (d, *J* = 7.8 Hz, 1H, ArH), 6.98 (t, *J* = 7.2 Hz, 1H, ArH), 7.32–7.44 [m(o), 2H, ArH], 7.73 (br s, 2H, ArH), 8.28 [d(o), *J* = 7.5 Hz, 1H, ArH], 8.36 [d(o), *J* = 7.5 Hz, 1H, ArH]; ¹³C NMR (CDCl₃, 75 MHz) δ 20.0, 59.5, 116.4, 116.8, 120.2, 120.6, 125.9, 126.7, 127.4, 127.6, 133.3, 134.3, 143.7, 146.7, 148.2, 160.1; MS (FAB, *m/z*) 264 (M⁺ + 1). Anal. Calcd for C₁₆H₁₃N₃O: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.16; H, 5.14; N, 16.09.

6-Phenyl-5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one (5d). A solution of **4a** (200 mg, 0.75 mmol) and SnCl₂·2H₂O (850 mg, 3.75 mmol) was dissolved in benzyl alcohol and heated at 90 °C for 1 h. The reaction mixture was concentrated in vacuo and diluted in ethyl acetate (10 mL). The organic layer was washed with saturated NaHCO₃ and a brine solution, and the resulting benzyl alcohol was evaporated by vacuum distillation. The solid was dried in vacuo, and the residue was purified by column chromatography (5% EtOAc in hexane) to provide **5d** as a reddish-brown solid. **5d**: 224 mg (92% yield); mp 188–189 °C; ¹H NMR (CDCl₃, 300 MHz) δ 5.14 (br s, 1H, –NH), 6.77 (d, *J* = 9 Hz, 1H, ArH), 6.94 (t, *J* = 7.8 Hz, 1H, ArH), 7.18–7.44 (m, 8H, ArH), 7.75 (br s, 2H, ArH), 8.31 (t, *J* = 8.4 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 75 MHz) δ 63.6, 116.3, 117.7, 120.5, 126.0, 126.1, 127.1, 127.5, 127.6, 128.5, 128.6, 133.4, 134.5, 139.2, 143.6, 147.1, 148.2, 160.7; MS (FAB, *m/z*) 326 (M⁺ + 1). Anal. Calcd for C₂₁H₁₅N₃O: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.41; H, 5.90; N, 14.31.

Acknowledgment. A.D.R. is thankful to CSIR, New Delhi, for providing a fellowship. The authors are highly grateful to Dr. A. K. Misra for his valuable suggestions during the course of the work.

Supporting Information Available: ¹H, ¹³C, DEPT90, DEPT135, COSY, and HSQC NMR spectra of **5a–j**, HMBC spectra of **5a**, **5e**, **5f**, **5i**, and **5j**, and ¹H NMR spectra of **2a**, **3a**, **4a**, and **4b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO0518912

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