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One-pot synthesis of 2-(2-hydroxyaryl)quinolines: reductive coupling reactions of 2′-hydroxy-2-nitrochalcones

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Abstract—A one-pot synthesis of novel 2-(2-hydroxyaryl)quinolines have been developed from the intramolecular reductive coupling reactions of 2′-hydroxy-2-nitrochalcones, induced by stannous chloride in acidic medium (HCl/AcOH). In some cases these transformations can be performed with ammonium formate/Pd–C in methanol.

Quinolines are six-membered heterocyclic compounds widely distributed in nature.[1] Due to the interesting and important biological properties and applications of quinoline derivatives (such as pharmaceuticals, polymers, cyanine dyes, antioxidants in the rubber industry and fungicides) many syntheses are reported in the literature for this type of compounds,[2] however the development of new and efficient methods for the preparation of these important molecules still continues to be an important and attractive area of research in synthetic organic chemistry.[3,4] In continuation of our interest in heterocyclic molecules,[5] we herein report a simple and facile one-pot synthesis of novel 2-(2-hydroxyaryl)quinolines **3** from 2′-hydroxy-2-nitro-chalcones **1**.

In the last decade, the cyclisation of 2′-aminochalcones has been stimulated since it originates 2-aryl-4-quinolone derivatives[2,6,7] which present important pharmacological activities.[7,8] More recently 2′-aminochalcones have been used in the preparation of 2-aryl-4-chloro-*N*-formyl-1,2-dihydroquinolines from their cyclisation under Vilsmeier conditions.[4] During our ongoing research program on the synthesis of aminochalcones and knowing that some quinolines can be made by intramolecular reactions of amino with carbonyl groups,[9,10] we decided to study the reduction of 2′-hydroxy-2-nitrochalcones **1**. 2-Aryl-quinolines have been obtained from palladium-catalysed coupling reactions of allylic alcohols or acetylenic carbinols with iodoanilines, from ruthenium-catalysed carbonylation of 2-nitrochalcones and from reductive coupling reactions of 2-nitrochalcones with low-valent titanium reagent ($TiCl_4$/Sm).[9] Some of these known methods for the synthesis of 2-arylquinolines have some disadvantages such as harsh reaction conditions, laborious work-up and low yields. To our best knowledge there are no reports on the synthesis of 2-(2-hydroxyaryl)quinolines, which can be used as good bidentate ligands in the complexation of transition metal ions. Here we report the first synthesis of 2-(2-hydroxyaryl)quinolines **3a–d** from the intramolecular reductive coupling reactions of the corresponding 2′-hydroxy-2-nitrochalcones **1a–d** induced by stannous chloride in hydrochloric acid and in some cases with ammonium formate–Pd/C in methanol.

The treatment of 2′-hydroxy-2-nitrochalcones **1a–d** with an excess of hydrated stannous chloride in hydrochloric acid led, after work-up, to the formation of two compounds when starting with chalcones **1a**,**b** and only one in the case of chalcones **1c**,**d**[11] (revealed by TLC analysis of the reaction mixture) (Scheme 1). The main spectroscopic characteristics of the product obtained in both cases are: (i) the presence of a hydroxyl group involved in a strong hydrogen bond (δ_H 14.93–15.34 ppm in the ^{1}H NMR spectra); (ii) the absence of double bonds in a *trans* configuration, well established in the ^{1}H NMR spectra of chalcones;[12] (iii) the absence of carbonyl groups in the ^{13}C NMR spectra; and (iv) molecular ions ($M^{+\bullet}$ in the EIMS) corresponding to the reduction of the nitro substituent into the amino group and the loss of one water molecule. All these spectro-

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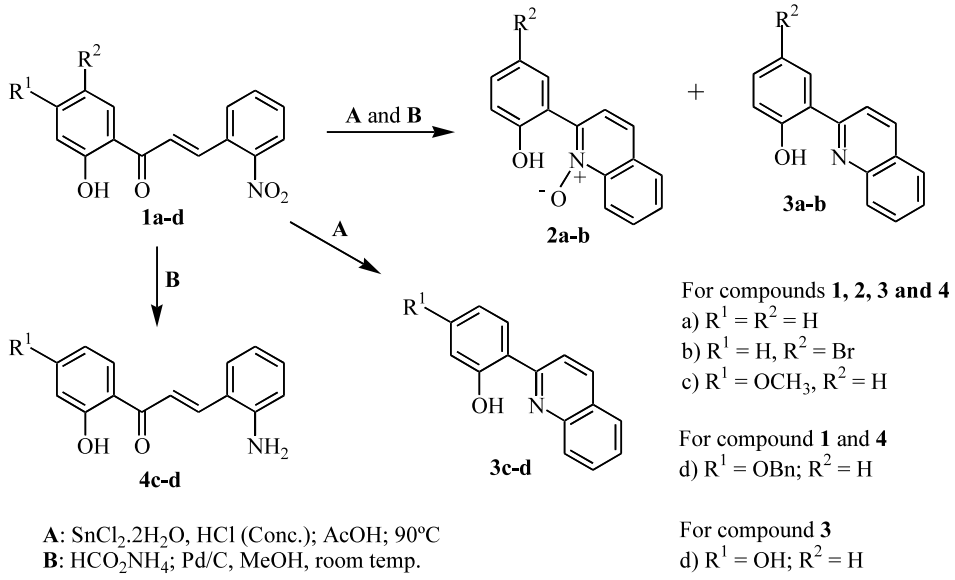
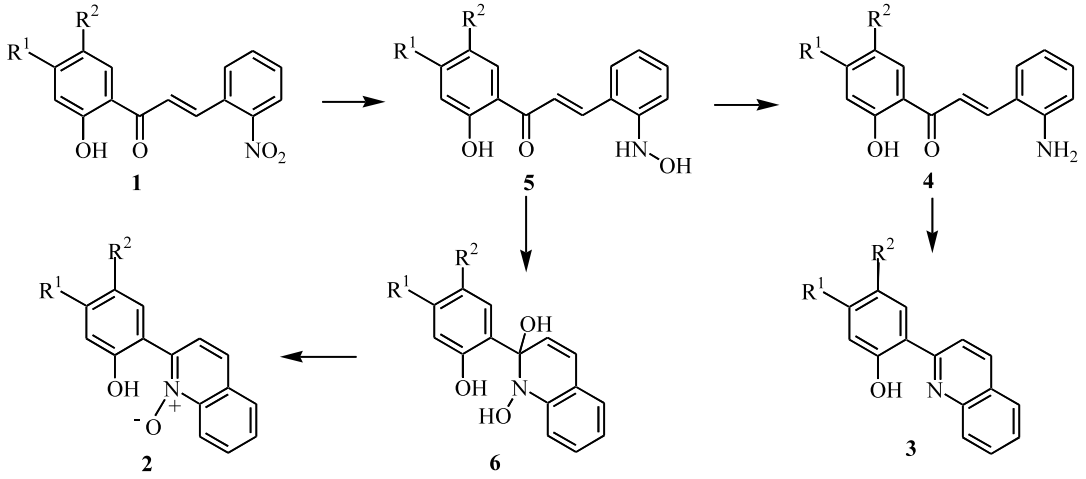


Scheme 1.

scopic data support the structure of novel 2-(2-hydroxyaryl)quinolines **3a**–**d**.[13] The second product obtained when starting with chalcones **1a**,**b** present similar spectroscopic features to those of **3a**–**d**, but the hydroxyl group involved in an hydrogen bond appear at lower frequency values (δ_H 11.30–11.37 ppm in the ^{1}H NMR spectra) and the molecular ions ($M^{+\bullet}$ in the EIMS) presents more 16 u.m.a. These data are only compatible with the structure of novel 2-(2-hydroxyaryl)quinoline-*N*-oxides **2a**,**b**.[14]

The results described above can be envisaged by the reaction mechanism depicted in Scheme 2: One of the intermediates in the reduction of 2-nitrochalcones **1** are hydroxylamine derivatives **5**.[15] In the case of electron donating substituents in the A ring (other than the OH involved in the intramolecular hydrogen bond) the reduction of these hydroxylamine derivatives **5c**,**d** into the 2-aminochalcones **4c**,**d** is favoured and followed by their acid-catalysed cyclodehydration into quinolines **3c**,**d**. In the case of starting with 4′-benzyloxy-2′-hydroxy-2-nitro-chalcone **1d** there also was the cleavage of the benzyloxy group, due to the presence of hydrochloric acid, giving the 2-(2,4-dihydroxyphenyl)quinoline **3d**.[16] The reduction of intermediates **5a**,**b** into the corresponding 2-amino-chalcones **4a**,**b** is probably slower and allowed the intramolecular attack of the hydroxylamine to the carbonyl group yielding intermediates **6a**,**b** which can then be reduced to the novel 2-(2-hydroxyaryl)quinoline-*N*-oxides **2a**,**b**.

The treatment of 2′-hydroxy-2-nitrochalcones **1c**,**d** with ammonium formate and Pd/C in methanol at room temperature for 3 h gave the corresponding aminochalcones **4c**,**d** (Scheme 1).[17,18] This means that in these conditions only the reduction of the nitro substituents occur; there was no reduction of the chalcone double bond and the benzyloxy group was not cleaved. However, the treatment of 2′-hydroxy-2-nitrochalcones **1a**,**b** with ammonium formate and Pd/C in the same condi-



Scheme 2.

tions yielded a mixture 2-(2-hydroxyaryl)quinolines **3a**,**b** (33–37%) and 2-(2-hydroxyaryl)quinoline-*N*-oxides **2a**,**b** (36–39%). These results confirm our hypothesis on the formation of quinoline-*N*-oxides **2a**,**b** in the reduction of nitrochalcones **1a**,**b**. The reduction of hydroxylamine derivatives **5a**,**b** is very slow, allowing the formation of intermediates **6a**,**b** and their reduction to quinoline-*N*-oxides **2a**,**b**, which can be reduced in these reaction conditions to the corresponding quinolines **3a**,**b**. This fact was confirmed by performing the reduction of quinoline-*N*-oxides **2a**,**b** into quinolines **3a**,**b** with ammonium formate and Pd/C in methanol at room temperature.

In conclusion we established a new one-pot synthesis of novel 2-(2-hydroxyaryl)quinolines from intramolecular reductive coupling reactions of 2′-hydroxy-2-nitro-chalcones. The application of this approach to the synthesis of other 2-arylquinolines in ongoing and will be reported in due course.

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References

1. Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp. 245–300 and references cited therein.
2. Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp. 167–243 and references cited therein.
3. (a) Meth-Cohn, O.; Goon, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 85–89; (b) Katritzky, A. R.; Arend, M. *J. Org. Chem.* **1998**, *63*, 9989–9991; (c) Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761–785; (d) Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693–3697.
4. Akila, S.; Selvi, S.; Balasubramanian, K. *Tetrahedron* **2001**, *57*, 3465–3469.
5. (a) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *New J. Chem.* **2000**, *24*, 85–92; (b) Pinto, D. C. G. A.; Silva, A. M. S.; Lévai, A.; Cavaleiro, J. A. S.; Patonay, T.; Elguero, J. *Eur. J. Org. Chem.* **2000**, 2593–2599; (c) Pinto, D. C. G. A.; Silva, A. M. S.; Almeida, L. M. P. M.; Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2002**, 3807–3815; (d) Sandulache, A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron* **2002**, *58*, 105–114.
6. (a) Donnelly, J. A.; Farrell, D. F. *J. Org. Chem.* **1990**, *55*, 1757–1761; (b) Varma, R. S.; Saini, R. K. *Synlett* **1997**, 857–858.
7. Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 3932–3936.
8. (a) Hirak, U.; Hisashi, Y.; Hiroshi, Y.; Hitoshi, T. *Eur. Pat. Appl. EP* 287951, *Chem. Abstr.* **1989**, *110*, 173109k; (b) Osawa, T.; Ohta, H.; Akimoto, K.; Harada, K.; Soga, H.; Jinno, Y. *Eur. Pat. Appl.* EP 343547, *Chem. Abstr.* **1990**, *112*, 235197g.
9. (a) Larock, R. C.; Kuo, M.-Y. *Tetrahedron Lett.* **1991**, *32*, 569–572; (b) Kundu, N. G.; Mahanty, J. S.; Das, P.; Das, B. *Tetrahedron Lett.* **1993**, *34*, 1625–1628; (c) Cenini, S.; Bettettini, E.; Fedele, M.; Tollari, S. *J. Mol. Catal. A: Chem.* **1996**, *111*, 37–41; (d) Ma, Y.; Zhang, Y. *J. Chem. Res.* **2001**, 108–109.
10. Boix, C.; de la Fuente, J. M.; Poliakoff, M. *New J. Chem.* **1999**, *23*, 641–643.
11. **Typical procedure with $SnCl_2{\cdot}2H_2O$ in HCl/AcOH**: A solution of hydrated stannous chloride (5.2 g, 23 mmol) in concentrated hydrochloric acid (20 mL) was added to a suspension of the appropriate 2′-hydroxy-2-nitrochalcone **1a**–**d** (5.7 mmol) in acetic acid (60 mL). The mixture was heated at 90°C for 4 h. After that period, the solution was cooled and treated with an excess of a 25% aqueous sodium hydroxide solution. The residue obtained was extracted with chloroform (2×50 mL) dried over Na_2SO_4 and evaporated to dryness. In the case of 4′-substituted-2′-hydroxy-2-nitrochalcones **1c**,**d**, the residue was purified by silica gel column chromatography, using chloroform as eluent, giving after evaporation and recrystallisation from ethanol 2-(2-hydroxyaryl)quinolines **3c**,**d** (**3c**, 66%; **3d**, 58%). For 2′-hydroxy-2-nitrochalcones **1a**,**b**, the obtained residue was purified by silica gel column chromatography, using as eluent 1:3 and 1:1 mixtures of chloroform-light petroleum to respectively collect 2-(2-hydroxyaryl)quinolines **3a**,**b** and 2-(2-hydroxyaryl)quinoline-*N*-oxides **2a**–**b** (**2a**, 47%; **3a**, 23%; **2b**, 44%; **3b**, 27%).
12. (a) Silva, A. M. S.; Tavares, H. R.; Barros, A. I. N. R. A.; Cavaleiro, J. A. S. *Spectrosc. Lett.* **1997**, *30*, 1655–1667; (b) Silva, A. M. S.; Cavaleiro, J. A. S.; Tarrago, G.; Marzin, C. *New J. Chem.* **1999**, *23*, 329–335; (c) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2003**, 747–755.
13. **Spectroscopic data for 2-(2-hydroxyphenyl)quinoline 3a**: mp: 109.8–110.7°C; ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 6.97–7.03 (m, 2H, H-3′ and H-5′), 7.41 (dt, 1H, H-4′, $J=1.2$ and 7.7 Hz), 7.67 (dt, 1H, H-6, $J=0.7$ and 7.7 Hz), 7.85 (dt, 1H, H-7, $J=1.1$ and 7.7 Hz), 8.05–8.10 (m, 2H, H-5 and H-8), 8.22 (dd, 1H, H-6′, $J=1.2$ and 7.7 Hz), 8.39 (d, 1H, H-3, $J=8.9$ Hz), 8.59 (d, 1H, H-4, $J=8.9$ Hz), 14.93 (s, 1H, O*H*); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 118.0 (C-3 and C-3′), 118.8 (C-1′), 118.9 (C-5′), 126.4 (C-4a), 127.0 (C-6 and C-8), 127.9 (C-6′), 128.0 (C-5), 130.9 (C-7), 132.2 (C-4′), 138.4 (C-4), 144.1 (C-8a), 157.7 (C-2), 160.2 (C-2′); EI-MS: m/z (rel. intensity) 221 ($M^{+\bullet}$, 100), 220 (59), 193 (25), 180 (15), 167 (30), 154 (7), 128 (16), 111 (8), 96 (10), 89 (4), 84 (15), 77 (9), 63 (7). Anal. calcd for $C_{15}H_{11}NO$: C, 81.45; H, 4.98; N, 6.33. Found: C, 81.40; H, 5.02; N, 6.30%.
14. **Spectroscopic data for 2-(2-hydroxyphenyl)quinoline-*N*-oxide 2a**: mp: 180.3–181.0°C; ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 7.05 (dd, 1H, H-3′, $J=1.0$ and 7.7 Hz), 7.10 (dt, 1H, H-5′, $J=1.0$ and 7.7 Hz), 7.53 (dt, 1H, H-4′, $J=1.6$ and 7.7 Hz), 7.69 (dd, 1H, H-6′, $J=1.6$ and 7.7 Hz), 7.87 (dt, 1H, H-6, $J=1.0$ and 7.8 Hz), 7.96 (d, 1H, H-3, $J=8.9$ Hz), 8.01–8.04 (m, 1H, H-7), 8.25 (d, 1H,

H-5, $J=7.8$ Hz), 8.35 (d, 1H, H-4, $J=8.9$ Hz), 8.75 (d, 1H, H-8, $J=8.7$ Hz), 11.30 (s, 1H, O*H*); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 119.0 (C-8), 119.6 (C-3′), 120.0 (C-5′), 121.4 (C-1′), 124.7 (C-3), 128.7 (C-5), 128.8 (C-4a), 129.2 (C-6), 130.2 (C-4), 132.1 (C-6′), 132.2 (C-7), 132.4 (C-4′), 139.9 (C-8a), 147.6 (C-2), 159.1 (C-2′); EI-MS: m/z (rel. intensity) 237 (M+$^{\bullet}$, 48), 221 (32), 220 (100), 208 (7), 191 (20), 180 (15), 165 (14), 140 (5), 128 (9), 102 (3), 95 (6), 77 (5), 63 (4). Anal. calcd for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64; N, 5.91. Found: C, 81.40; H, 5.02; N, 6.30%.

15. Roberts, J. S. In *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 2, pp. 184–217.
16. **Spectroscopic data for 2-(2,4-dihydroxyphenyl)quinoline 3d**: mp: 175.4–176.3°C; ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 6.36 (d, 1H, H-3′, $J=2.4$ Hz), 6.43 (dd, 1H, H-5′, $J=2.4$ and 8.7 Hz), 7.59 (dt, 1H, H-6, $J=0.9$ and 8.0 Hz), 7.76–7.82 (m, 1H, H-7), 7.96 (d, 1H, H-8, $J=8.0$ Hz), 7.99 (d, 1H, H-5, $J=8.0$ Hz), 8.02 (d, 1H, H-6′, $J=8.7$ Hz), 8.21 (d, 1H, H-3, $J=9.0$ Hz), 8.47 (d, 1H, H-4, $J=9.0$ Hz), 10.03 (s, 1H, O*H*-4′), 15.23 (s, 1H, O*H*-2′); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 103.5 (C-3′), 107.5 (C-5′), 110.8 (C-1′), 117.5 (C-3), 125.8 (C-4a), 126.3 (C-6), 126.5 (C-8), 128.0 (C-5), 129.2 (C-6′), 130.8 (C-7), 138.0 (C-4), 144.0 (C-8a), 158.0 (C-2), 161.2 (C-4′), 162.4 (C-2′); EI-MS: m/z (rel. intensity) 237 (M+$^{\bullet}$, 92), 236 (64), 207 (33), 191 (3), 180 (36), 167 (9), 128 (12), 105 (100), 89 (11), 77 (67), 63 (15). Anal. calcd for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64; N, 5.91. Found: C, 81.40; H, 5.02; N, 6.30%.
17. **Typical procedure HCO_2NH_4, Pd/C**. To a stirred suspension of the appropriate 2′-hydroxy-2-nitrochalcone **1a–d** (5 mmol) and 10% Pd/C (0.2–0.3 g) in dry methanol (10 mL) at room temperature was added anhydrous ammonium formate (23 mmol) in a single portion under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 3 h. The catalyst was removed by filtration through Celite pad and washed with methanol (2×10 mL). The filtrate was evaporated under reduced pressure and the residue dissolved in chloroform and washed with water (3×25 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. In the case of 4′-substituted-2′-hydroxy-2-nitrochalcones **1c**,**d**, the residue was recrystallised from ethanol, giving 2-amino-2′-hydroxychalcones **4c**,**d** (**4c**, 68%; **4d**, 50%). For 2′-hydroxy-2-nitrochalcones **1a**,**b**, the obtained residue was purified by silica gel column chromatography, using as eluent 1:3 and 1:1 mixtures of chloroform-light petroleum to respectively collect 2-(2-hydroxyaryl)quinolines **3a**,**b** and 2-(2-hydroxyaryl)quinoline-*N*-oxides **2a–b** (**2a**, 36%; **3a**, 33%; **2b**, 39%; **3b**, 37%).
18. **Spectroscopic data for 2′-amino-4′-methoxychalcone 4c**: mp: 156.7–157.9°C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 3.86 (s, 3H, OCH_3), 4.09 (s, 2H, NH_2), 6.47 (s, 1H, H-3′), 6.50 (dd, 1H, H-5′, $J=2.5$ and 9.6 Hz), 6.74 (d, 1H, H-3, $J=7.6$ Hz), 6.81 (t, 1H, H-5, $J=7.6$ Hz), 7.22 (dt, 1H, H-4, $J=1.2$ and 7.6 Hz), 7.50 (d, 1H, H-6, $J=7.6$ Hz), 7.51 (d, 1H, H-α, $J=15.2$ Hz), 7.82 (d, 1H, H-6′, $J=9.6$ Hz), 8.05 (d, 1H, H-β, $J=15.2$ Hz), 13.52 (s, 1H, O*H*); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 55.6 (O*C*H$_3$), 101.0 (C-3′), 107.7 (C-5′), 114.1 (C-1′), 116.9 (C-3), 118.9 (C-5), 120.1 (C-α), 120.2 (C-1), 128.2 (C-6), 131.2 (C-6′), 131.8 (C-4), 139.7 (C-β), 146.3 (C-2), 166.1 (C-4′), 166.7 (C-2′), 191.8 (C=O); EI-MS: m/z (rel. intensity) 269 (M$^{+\bullet}$, 27), 252 (62), 251 (100), 250 (38), 222 (8), 208 (11), 180 (10), 151 (33), 146 (16), 128 (15), 118 (34), 108 (12), 91 (17). Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.38; H, 5.58; N, 5.20. Found: C, 81.40; H, 5.02; N, 6.30%.