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REACTIONS of NITROBENZO[*c*]CINNOLINES with HYDROXYLAMINE

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ABSTRACT

The reaction of 1-nitrobenzo[*c*]cinnoline with hydroxylamine in the presence of potassium hydroxide in ethanol gave the corresponding 2- and 4-amino derivatives. The reaction of 2-nitrobenzo[*c*]cinnoline 6-oxide with hydroxylamine under the same conditions yielded 2-nitrosobenzo[*c*]cinnoline 6-oxide. Mononitration of *N*-acetylbenzo[*c*]cinnolin-2-amine occurred at position 1.

1. INTRODUCTION

Amino substituted aromatic heterocyclic compounds are important intermediates in organic synthesis and industry. The vicarious nucleophilic substitution (VNS) of hydrogen with amino group for electrophilic nitroarenes and nitro-substituted heterocycles offers a great facility. Synthesis of nitroaryl-hetaryl amines via VNS of hydrogen are among the more convenient methods.[1]

Benzo[*c*]cinnoline and some of its derivatives are useful intermediates for the manufacturing of dyes,[2] colored polyamide fibers,[3] charge-generating agents for electrophotographic photoreceptors,[4] electrochromic polymers.[5] In addition, it is reported that some benzo[*c*]cinnoline derivatives have herbicidal[6] and microbial activities.[7]

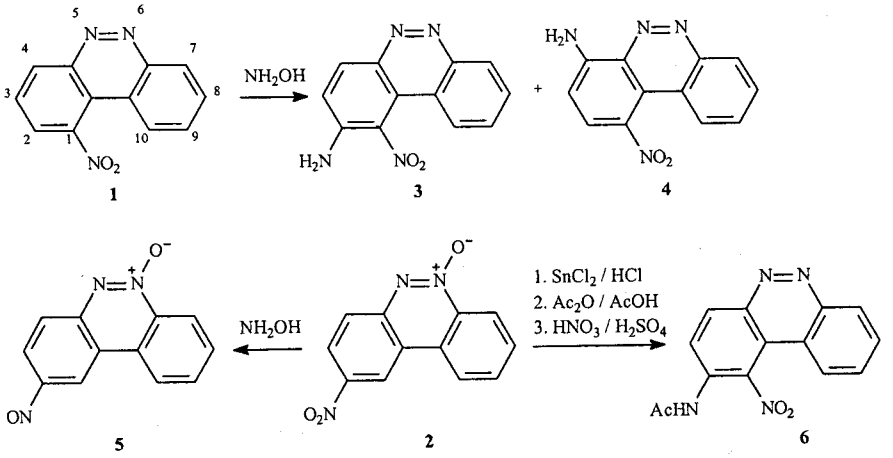
Up to now, in amination of electrophilic nitroarenes via VNS reactions, a variety of agents have been used, such as 4-amino-1,2,4-triazole,[8] *O*-methylhydroxylamine,[9] sulfenamides,[1] 1,1,1-trimethylhydrazinium iodide,[10] hydrazine and hydroxylamine.[1] However, the reactions of 1-aryl-4-nitroimidazoles with hydroxylamine in the presence of KOH or MeONa in MeOH yielded no trace of corresponding amine derivatives, while 1-methyl-4-nitroimidazoles gave the VNS products in moderate yields.[11]

Aminations via VNS reactions of nitro-substituted six-membered heteroaromatics with hydroxylamine in basic media are very limited, e.g. amination

of 6-nitroquinoxalines,[12] and 3-nitrocinnoline.[13] It was, however, reported that direct amination of nitropyridines with *O*-methylhydroxylamine was performed in the presence of zinc catalyst, but failed to proceed without it.[9]

Generally, aminobenzo[*c*]cinnolines have been prepared by the reduction of corresponding nitrobenzo[*c*]cinnolines, or by reductive cyclizations of trinitrobiphenyls,[14] or amino-substituted 2,2'-dinitrobiphenyls.[15] On the other hand, the reported aromatic nucleophilic substitution reactions of halogenobenzo[*c*]cinnolines are those with potassium amide,[16] alkoxides,[17] dialkyl amines[18] and their salts,[19] and pyrrolidine, piperidine and morpholine.[20] The reactions of benzo[*c*]cinnoline and chlorobenzo[*c*]cinnolines with lithium dimethylamide in dimethylamine led to the formation of complex product mixtures.[19] Fluorodenitrations of nitrobenzo[*c*]cinnolines with tetrabutylammonium fluoride have also been reported.[21]

The aim of this study has been the amination of nitrobenzo[c]cinnolines with hydroxylamine via one-pot vicarious nucleophilic substitution of hydrogen.



RESULTS AND DISCUSSION

As far as we know, there is no report in the literature about VNS reactions of nitrobenzo[*c*]cinnolines and nitration of aminobenzo[*c*]cinnolines. The reactions of 1-nitrobenzo[*c*]cinnoline with hydroxylamine gave the corresponding 2- and 4-amino derivatives (**3** and **4**), at 10-11°C and 55-56°C, at the ratio *ca.* 8/1 and 1/4 respectively, the isomers were isolated by column chromatography. 1-Nitrobenzo[*c*]cinnolin-2-amine (**3**) has also been obtained from the nitration of *N*-

acetylbenzo[*c*]cinnolin-2-amine (**7**) and subsequent hydrolysis of the resulting *N*-acetyl-1-nitrobenzo[*c*]cinnolin-2-amine (**6**). The reduction of 2-nitrobenzo[*c*]cinnoline 6-oxide (**2**) with hydroxylamine to 2-nitrosobenzo[*c*]cinnoline (**5**) occurred instead of VNS reaction. The reduction of **5** with $SnCl_2$/HCl in ethanol at room temperature yielded 2-aminobenzo[*c*]cinnoline (**8**),[14] and with hydrazine in the presence of Pd-C gave 2-aminobenzo[*c*]cinnoline 6-oxide (**9**). Amination reactions of **1** with hydroxylamine proceeded at temperatures of 10, 25, 40, and 55°C, and were monitored by TLC; decomposition products increased while the isomer ratio (**3**/**4**) decreased at temperatures above 25°C. In this study, it is reported that : a) **3** can be prepared from the VNS reaction of **1** with hydroxylamine in basic ethanol at 10-11°C in moderate yield, b) synthesis of **5** from the reduction of **2** with the yield 62%, c) the nitration of **7** yields corresponding 1-nitro derivative (**6**), and d) hydrolysis of **6** in aq. HCl/ethanol mixture gives **3**. The structures of products (**3-6**) were established by their spectra (^{1}H, ^{13}C, and ^{1}H-^{1}H COSY NMR). ^{1}H NMR spectral data of compounds (**7**, **8** and **9**) are reported in experimental for comparison.

The products (**3-6**) are new and may provide several ways for their utilizations, making them interesting intermediates in heterocyclic synthesis.

EXPERIMENTAL

Melting points are uncorrected. IR Spectra were recorded in KBr on a Mattson 1000 FTIR spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker DPX FT-NMR (400 MHz) spectrometer ($SiMe_4$, as internal standard). Mass spectra were recorded on PLATFORM II LC-MS spectrometer. Column chromatography was performed using silica gel 230-400 mesh (Merck). The compounds (**1**, **2**, and **8**)[14] were prepared from benzo[*c*]cinnoline and benzo[*c*]cinnoline 5-oxide[20] by known methods. Other reagents are available commercially.

General procedure for the amination reactions of 1-nitrobenzo[c]cinnoline (1) To a stirred mixture of compound **1** (0.23 g, 1.0 mmol) and hydroxylamine hydrochloride (0.60 g, 8.6 mmol) in ethanol (25 mL) at 10-11°C, KOH (1.25 g, 22.3 mmol) in water (3 mL) was added dropwise during 15 minutes at 10-11°C. After 2 h stirring at the same temperature, the mixture was diluted with cold water and neutralized with HCl. Precipitated product was collected and recrystallized from ethanol to yield 1-nitrobenzo[*c*]cinnolin-2-amine (**3**) (0.16 g; 67%). The mother liquor was evaporated under vacuum, and the residue was chromatographed on silica gel with $CHCl_3$/i-PrOH (50/1). The first fraction gave **4** (30 mg, 13%), second fraction gave **3** (10 mg). For the synthesis of **4** as major product, reaction proceeded at 55-56°C for 1 h. The reaction mixture was diluted with water, and neutralized with HCl. Precipitated product was collected, and crystallized from ethanol-water, and from toluene respectively, to give 1-nitrobenzo[*c*]cinnolin-4-amine (**4**) (75 mg,

31%). The isomers **3** and **4** in mother liquor were isolated by column chromatography as given above.

1-Nitrobenzo[*c*]cinnolin-2-amine (3)
Pale yellow crystals, mp 282-283°C (decomp) (ethanol). ^{1}H NMR ($CDCl_3$-dmso-d_6) δ 8.50 (dd, J = 8.4 Hz, J = 0.8 Hz, 7-H), 8.36 (d, J = 9.2 Hz, 4-H), 7.87 (dd, J = 8.5 Hz, 10-H), 7.81 (td, J = 7.6 Hz, J = 0.9 Hz, 8-H), 7.67 (td, J = 7.7 Hz, J = 1.3 Hz, 9-H), 7.43 (d, J = 9.2 Hz, 3-H), 7.10 (bs, 2H, NH_2). ^{13}C NMR ($CDCl_3$-dmso-d_6) δ 147.1, 146.9, 139.8, 136.1, 131.2, 130.6, 130.4, 124.5, 122.2, 117.7, 117.6 (one peak was obscured). IR: ν_{max} 3442, 3391 and 3297 (N-H), 3156, 3059, 1636, 1517 (NO_2) cm^{-1}. Anal. Calcd for $C_{12}H_8N_2O_4$: C, 60.00; H, 3.33; N, 23.33. Found: C, 59.85; H, 3.35; N, 23.12. MS *m/z* 240 (M^+, 100), 241 (15), 242 (2), 210 (16), 139 (76).

1-Nitrobenzo[*c*]cinnolin-4-amine (4)
Yellow crystals, mp 226-227°C. ^{1}H NMR ($CDCl_3$-dmso-d_6) δ 8.57 (dd, J = 8.2 Hz, J = 0.9 Hz, 7-H), 8.08 (d, J = 8.8 Hz, 2-H), 8.04 (dd, J = 8.7 Hz, J = 0.7 Hz, 10-H), 7.88 (td, J = 8.2 Hz, J = 1.2 Hz, 8-H), 7.74 (td, J = 7.8 Hz, J = 1.3 Hz, 9-H), 7.52 (bs, 2H, NH_2), 6,98 (d, J = 8.9 Hz, 3-H). ^{13}C NMR ($CDCl_3$-dmso-d_6) δ 153.4, 147.4, 133.8, 132.8, 132.5, 131.2, 131.1, 131.0, 125.9, 117.8, 116.9, 109.2. IR: ν_{max} 3438, 3288 and 3208 (N-H), 3155, 3072, 1638, 1586, 1548, 1491, 1354 (NO_2) cm^{-1}. Anal. Calcd for $C_{12}H_8N_2O_4$: C, 60.00; H, 3.33; N, 23.33. Found: C, 59.78; H, 3.30; N, 23.05. MS *m/z* 240 (M^+, 100), 242 (24), 210 (47), 139 (46).

2-Nitrosobenzo[c]cinnoline 6-oxide (5)
Compound **2** (0.24 g, 1 mmol) was treated as described above for **3**. The reaction mixture was diluted with water and neutralized with HCl. Precipitated product was collected, washed with water and dried in air. The crude product (0.14 g, 62 %) was sufficiently pure for further experiments; mp 189-190°C (decomp). ^{1}H NMR ($CDCl_3$-dmso-d_6) δ 9.76 (d, J = 1.8 Hz, 1-H), 8.97 (d, J = 8.0 Hz, 7-H), 8.87 (d, J = 8.6 Hz, 10-H), 8.22 (td, J = 7.7 Hz, J = 1.1 Hz, 8-H), 8.09 (d, J = 8.8 Hz, 4-H), 8.05 (td, J = 7.9 Hz, J = 1.1 Hz, 9-H), 7.70 (dd, J = 8.8 Hz, J = 1.9 Hz, 3-H). ^{13}C NMR ($CDCl_3$-dmso-d_6) δ 157.3, 141.0, 133.6, 129.4, 127.0, 124.9, 123.1, 118.7, 118.3, 118.1, 114.5, 112.3. IR: ν_{max} 3082, 1610, 1585, 1485, 1458, 1402, 1316 cm^{-1}. Anal. Calcd for $C_{12}H_7N_3O_2$: C, 64.00; H, 3.11; N, 18.67. Found: C, 64.30; H, 3.00; N, 18.54. MS *m/z* 225 (M^+, 25), 226 227, 140 (100).

N-Acetyl-1-nitrobenzo[c]cinnolin-2-amine (6)
Compound **7** (0.24 g, 1 mmol) in conc. H_2SO_4 (2 mL) was treated with nitric acid (d 1.4, 1 mL) in conc. H_2SO_4 (2 mL) at 0°C. The solution was kept at 5-10°C for 2 h., and then poured on ice. The crude product; washed, dried, crystallized from aq AcOH, and sublimed under reduced pressure (20 torr) at 220°C to give **6** (0.13 g, 46 %), white needles, mp 252-253°C. ^{1}H NMR ($CDCl_3$) δ 8.68 (d, J = 9.2 Hz, 4-H),

8.63 (d, J = 9.3 Hz, 3-H), 8.61 (dd, J = 8.3 Hz, J = 1.1 Hz, 7-H), 8.03 (bs, 1H, NH), 7.83 (d, J = 8.5 Hz, 10-H), 7.78 (td, J = 7.6 Hz, J = 1.0 Hz, 8-H), 7,66 (td, J = 7.8 Hz, J = 1.4 Hz, 9-H), 2.13 (s, 3H, CH_3). IR: ν_{max} 3381 (N-H), 3080, 2927, 1667 (C=O), 1610, 1538 and 1369 (NO_2) cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_4O_3$: C, 59.58; H, 3.58; N, 19.84. Found: C, 59.70; H, 3.47; N, 19.66. MS *m/z* 282 (M^+), 283, 236 (100).

N-Acetylbenzo[*c*]cinnolin-2-amine (7)

The suspension of **8** (0.39 g, 2 mmol) in Ac_2O (20 mL) was stirred at room temperature overnight. The crude product was crystallized from aq. AcOH to give **7**, mp 240-241°C (lit.[14]: mp 239-240°C). ^1H NMR ($CDCl_3$) δ 8.98 (d, 1-H), 8.51 (m, 7-H), 8.47 (d, J = 8.9 Hz, 4-H), 8.38 (m, 10-H), 7.70 (m, 2H, 8- and 9-H), 7.56 (bs, 1H, NH), 7,50 (dd, J = 8.9 Hz, J = 2.2 Hz, 3-H), 2.13 (s, 3H, CH_3CO).

2-Aminobenzo[c]cinnoline (8)

Compound **5** was reduced by SnCl/HCl in ethanol to give **8** according to known method.[14] mp 244-245°C (lit.[14] 244-245°C). ^1H NMR ($CDCl_3$-methanol-d_4) δ 8.43 (m, 2H, 7- and 10-H), 8.30 (d, J = 8.9 Hz, 4-H), 7.81(m, 2H, 8- and 9-H), 7.55 (d, J = 2.3 Hz, 1-H), 7.26 (dd, J = 8.9 Hz, J = 2.4 Hz, 3-H).

2-Aminobenzo[c]cinnoline 6-oxide (9)

Compound **5** (0.23 g, 1 mmol) was reduced by hydrazine hydrate (0.3 mL, 80%) and Pd-C (10 mg, 10% Pd) in ethanol (20 mL) at room temperature. The mixture was filtered, diluted with water. Precipitated product was collected and crystallized from ethanol-water to give **9**, mp 214-215°C (decomp) [lit.[14] 213-215°C (decomp)]. ^1H NMR ($CDCl_3$-methanol-d_4) δ 8.86 (dd, J = 8.5 Hz, J = 0.7 Hz, 7-H), 8.49 (d, J = 8.2 Hz, 10-H), 7.97 (td, 1H, 8-H), 7.91 (td, 1H, 9-H), 7.87 (d, J = 8.8 Hz, 4-H), 7.59 (d, J = 2.3 Hz, 1-H), 7.25 (dd, J = 8.9 Hz, J = 2.4 Hz, 3-H).

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