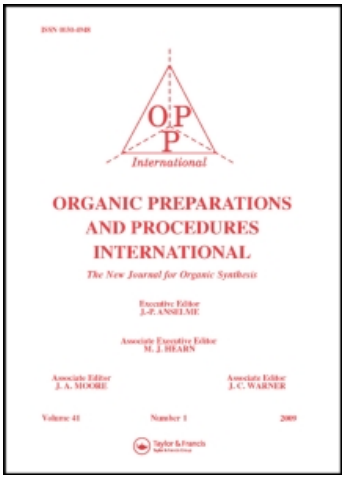

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IMPROVED PROCEDURES FOR THE PREPARATION OF BENZO[c]CINNOLINE, ITS N-OXIDE AND SOME BROMO DERIVATIVES AND SYNTHESIS OF PYRROLIDINO, PIPERIDINO, AND MORPHOLINOBENZO[c]CINNOLINES

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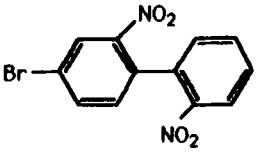
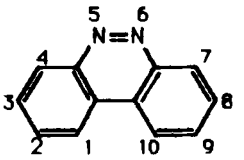
The most widely used method of preparing benzo[c]-cinnolines is the reductive cyclisation of 2,2′-dinitro-biphenyls,[1-8] e.g., the reduction of 2,2′-dinitrobiphenyl (1) with Raney nickel/H_2[5] or Pd-C/H_2[6] to benzo[c]cinnoline (2) or with sodium sulfide[7] to benzo[c]cinnoline-N-oxide (3). Depending on the reaction conditions, the reduction of 1 with Raney



1a



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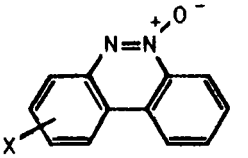
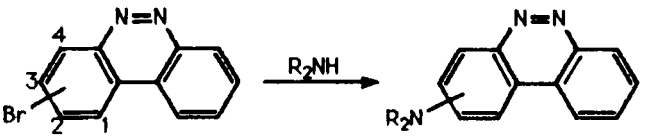


3: X = H
3a: X = 2-Br
3b: X = 4-Br



4 5 - 7

4	5	6	7
a: 1-Br	a: 1-Pyrrolidino	a: 1-Piperidino	a: 1-Morpholino
b: 2-Br	b: 2-Pyrrolidino	b: 2-Piperidino	b: 2-Morpholino
c: 3-Br	c: 3-Pyrrolidino	c: 3-Piperidino	c: 3-Morpholino
d: 4-Br	d: 4-Pyrrolidino	d: 4-Piperidino	d: 4-Morpholino

R_2NH: Pyrrolidine, piperidine, and morpholine

nickel/hydrazine[3] gives 2 or 3. Recently, it was reported that 2, 3 or benzo[c]cinnoline-N,N′-dioxide could be obtained from the reduction of 1 with $NaBH_4$-Pd in NaOH media by varying the $NaBH_4$/NaOH ratio. It was reported that mixed products are formed by the reduction of 1 with Pd-C/hydrazine.[2-4] Although formation of 3 from the reduction of 1 with Pd-C (5% Pd)/hydrazine was mentioned, no procedure was given.[9]

There are several methods for the preparation of monobromobenzo[c]cinnolines.[10-13] 2-Bromobenzo[c]cinnoline (4b) has been prepared from either 2-aminobenzo[c]cinnoline by a Sandmeyer reaction[10] or by the reduction of 2-bromobenzo[c]cinnoline-6-oxide (3a) with lithium aluminium hydride[11] or with stannous chloride;[12] Compound 3a has also been isolated from the Sandmeyer reaction of 2-aminobenzo[c]cinnoline-6-oxide,[10] and also from 2-acetamido-2′-nitrobiphenyl[12] by bromination, hydrolysis, and cyclisation of the resulting 2-amino-5-bromo-2′-nitrobiphenyl with base. Synthesis of 4b has also been achieved by the oxidative cyclisation of 2,2′-diamino-5-bromobiphenyl, obtained from 2,2′-diacetamidobiphenyl by bromination and subsequent hydrolysis of the resulting 2,2′-diacetamido-5-bromobiphenyl[10]. 3-Bromobenzo[c]cinnoline (4c) has been prepared by the reductive cyclisation of 4-bromo-2,2′-dinitrobiphenyl (1a) which was isolated from the reaction products of a mixed Ullmann reaction between 1,4-dibromo-2-nitrobenzene and 2-nitrobromobenzene.[12] There is no report in the literature documenting a synthetically useful reduction of 1 with Pd-C/hydrazine to give 2 and 3, or the direct brominations of 1 and 3.

The only reported aromatic nucleophilic substitution reactions of halobenzo[c]cinnolines are those with potassium

amide,[14] alkoxides,[15] sodium anilide,[16] dialkylamines[17] (diethyl and dimethylamines) and their salts.[18] Reactions of monochlorobenzo[c]cinnolines with dialkylamines gave the four corresponding dimethylaminobenzo[c]cinnolines and 2-diethylaminobenzo[c]cinnoline at high temperature and under pressure;[17] similar reaction with lithium dimethylamide in dimethylamine led to the formation of complex product mixtures.[18]

We now report: a) 2 and 3 can be prepared in high yields (over 90%) from the reduction of 1 with hydrazine in the presence of Pd-C (10% Pd) catalyst. In basic ethanol, 2 is formed, while in neutral ethanol 3 is produced. This procedure requires very little catalyst and small amounts of ethanol; b) 4b and

TABLE 1. Yields and Analytical Data of Compounds 5-7.

Compd No	Time (hrs)	Yield (%*)	mp (°C)	Analyses, Found (Calcd.) C	H	N
5a	96	52[a]	94-95	77.10(77.08)	6.17(6.06)	16.58(16.85)
5b	12	80[c]	238-239	77.20(77.08)	6.14(6.06)	16.80(16.85)
5c	192	70[e]	219-220	77.05(77.08)	6.04(6.06)	16.91(16.85)
5d	8	80[f]	117-118	77.39(77.08)	6.01(6.06)	16.57(16.85)
6a	144	59[b]	124-125	77.63(77.54)	6.55(6.51)	16.01(15.96)
6b	48	72[d]	135 136	77.68(77.54)	6.65(6.51)	15.69(15.96)
6c	216	59[e]	150-151	77.64(77.54)	6.61(6.51)	15.87(15.96)
6d	14	76[g]	145-146	77.53(77.54)	6.44(6.51)	16.11(15.96)
7a	144	55[a]	158-159	72.61(72.43)	5.84(5.70)	15.61(15.84)
7b	48	75[d]	193-194	72.51(72.43)	5.65(5.70)	15.72(15.84)
7c	216	49[e]	227-228	72.67(72.43)	5.73(5.70)	15.65(15.84)
7d	16	76[h]	138.5	72.32(72.43)	5.66(5.70)	16.10(15.84)

*Recrystallisation solvents; a) p.ether-Et_2O b) n-Hexane-Et_2O c)EtOH d) Benzene e) 2-Propanol f) CH_2Cl_2-EtOH g) n-Hexane-EtOH h) n-Hexane-CH_2Cl_2.

TABLE 2. Mass Spectra and ^1H NMR data for Compounds 5-7.

Compd No	Found M^+ (Required M)	$\delta_{arom.}$/ppm	$\delta_{aliph.}$/ppm
5a	249(249)	7.47-9.33 (m, 7H)	2.10 (bs, 4H) 2.75 (bs, 2H) 3.54 (bs, 4H)
5b	249(249)	7.14-8.57 (m, 7H)	2.13 (m, 4H) 3.52 (t, 4H)
5c	249(249)	7.20-8.60 (m, 7H)	2.10 (m, 4H) 3.46 (t, 4H)
5d	249(249)	6.81-8.52 (m, 7H)	2.44 (m, 4H) 3.94 (m, 4H)
6a	263(263)	7.59-9.98 (m, 7H)	1.42-1.98 (m, 6H) 2.71-3.34 (m, 4H)
6b	263(263)	7.44-8.56 (m, 7H)	1.71 (m, 6H) 3.49 (t, 4H)
6c	263(263)	7.56-8.61 (m, 7H)	1.70 (m, 6H) 3.41 (t, 4H)
6d	263(263)	7.25-8.68 (m, 7H)	1.72 (m, 2H) 1.96 (m, 4H) 3.54 (t, 4H)
7a	265(265)	7.60-9.96 (m, 7H)	3.03-3.19 (m, 4H) 4.04 (m, 4H)
7b	265(265)	7.45-8.60 (m, 7H)	3.46 (t, 4H) 3.94 (t, 4H)
7c	265(265)	7.58-8.65 (m, 7H)	3.42 (t, 4H) 3.96 (m, 4H)
7d	265(265)	7.21-8.67 (m, 7H)	3.61 (t, 4H) 4.09 (t, 4H)

bs: broad singlet, m: multiplet, t: triplet.

4-bromobenzo[c]cinnoline(4d) may be obtained by the bromination of 3 using bromine in the presence of silver acetate and subsequent reduction of the resulting products (2-and 4-bromobenzo-[c]cinnoline-6-oxides, 3a and 3b) with Raney nickel/hydrazine in refluxing ethanol. Compounds 3a and 3b were also obtained by the bromination of 3 in the presence of iron-powder at 140-150°; c) 4c was prepared by bromination of 1 in the presence of iron-powder at 140-150°, followed by reductive cyclisation of the resulting 4-bromo-2,2′-dinitrobiphenyl (1a) with hydrazine in the presence of Raney nickel in refluxing ethanol; d) the synthesis of 1-, 2-, 3- and 4-pyrrolidino, piperidino, and morpholinobenzo[c]cinnoline derivatives (5-7) from the reaction

of the corresponding bromobenzo[c]cinnolines with an excess of amine (pyrrolidine, piperidine, and morpholine). In the case of 4a and 4c, small amounts of dimethyl sulfoxide was added to the reaction medium to increase the rate of the reaction.[18,20]

It is known that reactions of chlorobenzo[c]cinnolines with dialkylamines (diethyl and dimethylamines) require high temperature and pressure.[17] We have observed that the reaction of 4 with cyclic secondary amines (pyrrolidine, piperidine, and morpholine) proceeded at refluxing temperature. It is reported that 2 has mutagenic activity.[21] The aim of this study is to synthesize new benzo[c]cinnoline derivatives which may have physiological activity.

EXPERIMENTAL SECTION

1-Bromobenzo[c]cinnoline (4a) was prepared by the method described by Barton and Lapham.[12] All mps (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Column chromatography was carried out by using Merck silica gel 60 (0.040-0.0063 mm). Merck F-254 thin-layer plates were used in order to follow the progress of the reactions, the purity of substance and column fractions. The spots of substances on the thin-layer were visualized under UV light. The 400 MHz ^{1}H NMR spectra of 2, 5a, 6a and 7a, and mass spectra of (5-7) were taken by Merck Laboratories, New Jersey, USA.The 200 MHz ^{1}H NMR spectra and elemental analyses were performed by Technological Research Council (TUBiTAK) Laboratories, Gebze, Turkey. The ^{1}H NMR spectra were recorded in $CDCl_3$ with Me_4Si, as internal reference. 2,2´-dinitrobiphenyl 1 (> 98%, Merck), Pd-C (10% Pd, Fluka), Raney nickel (Ni-Al alloy, 50% Ni, Merck).

Benzo[c]cinnoline (2).- Hydrazine hydrate (15.5 g, 80%) was added to a mixture of 1 (6.0 g, 25 mmol), Pd-C (0.1 g, 10% Pd) and sodium hydroxide (0.4 g) in ethanol (20 ml) with continuous stirring. A vigorous reaction ensued within a short time. The reaction mixture was refluxed for 2 hrs. The hot solution was filtered, cooled and neutralized with conc. hydrochloric acid. The bright yellow solid which had precipitated was collected to give 4.1 g (93%) of 2, which was recrystallized from ethanol

mp. 158-159°, lit.[6] 156°; no mp. depression was observed with an authentic sample. ^{1}H NMR ($CDCl_3$): δ 8.77 (m, 2H, H4 and H7), 8.60 (m, 2H, H1 and H10), 7.93 (m, 4H, H2, H3, H8 and H9).

Benzo[c]cinnoline-N-oxide (3).- Hydrazine hydrate (36.7 g, 80%) was added slowly to a mixture of 1 (18.6 g, 76 mmol) and Pd-C (0.2 g, 10% Pd) in hot ethanol (90 ml) with stirring, and the mixture was refluxed for 2 hrs. The hot solution was filtered and diluted with water (30 ml). The pale yellow product which precipitated, was collected to give 14.0 g (94%) of 3, which was recrystallized from ethanol-water, mp. 138-139°, lit.[7] 138°; no mp. depression was observed with an authentic sample.

2- and 4-Bromobenzo[c]cinnoline-6-oxides (3a and 3b).- (i) Bromine (4.7 g) in glacial acetic acid (5 ml) was added to a mixture of 3 (3.9 g, 20 mmol), silver acetate (4.0 g) and conc. sulfuric acid (2 ml) in glacial acetic acid (30 ml), and stirred for 5 hrs at room temperature. The reaction mixture was poured into cold water; the precipitated product was collected, treated with 100-130 ml of hot methanol, filtered to remove the silver salts and the solution was evaporated. The residue was chromatographed on a silica gel column (120 g), and eluted with dichloromethane. The first eluate (80 ml) gave 1.0 g (24%) of 3b, mp. 244-245°, lit.[13] 234 235°, after recrystallization from dichloromethane-ethyl acetate.

Anal. Calcd. for $C_{12}H_7BrN_2O$: C, 52.39; H, 2.56; N, 10.18

Found: C, 52.41; H, 2.48; N, 9.97

The second fraction gave 1.4 g (33 %) of 3a, which was recrystallized from dichloromethane-petroleum ether (bp. 40-60°), mp. 251-252°,lit.[10] 249-250°. Starting material (3) was recovered from the last fraction (0.9 g).

(ii).- Bromine (1.3 g) was added dropwise to a mixture of 3 (1.0 g, 5.1 mmol) and iron-powder (0.1 g) at 140-150° with stirring, the rate of addition being adjusted to avoid loss of bromine. The mixture was heated at 140-150° until bromine vapour disappeared. After cooling, the solid was dissolved in hot methanol (50 ml), the solution filtered by gravity and the product was precipitated with water. The isomers (3a and 3b) were separated and purified as in (i), yields for 3a 0.3 g (27%) for 3b 0.4 g (36%). The amount of recovered starting material (3) was 0.2g.

4-Bromo-2,2´-dinitrobiphenyl (1a).- Reaction were carried out using a procedure similar to that described above for 3a and 3b (ii). In this reaction, bromine (4.4 g), 1 (5.0 g, 21 mmol) and iron-powder (0.2 g) were used. The crude product was chromatographed on a silica gel column in petroleum ether-benzene (1:1). First fraction gave 0.3 g (4%) of 4,4´-dibromo-2,2´-dinitrobiphenyl which was recrystallized from ethanol, mp. 166.5-167°; lit.[11] 150°. ^{1}H NMR ($CDCl_3$): δ 7.16 (d, 2H, H1 and H10), 7.83 (dd, 2H, H2 and H9), 8.33(d, 2H, H4 and H7), J_{1-2} 8.19 Hz, J_{2-4} 2.02 Hz. The second fraction gave 2.9 g (43%) of 1a, which was recrystallized from methanol, mp. 148-148.5°; lit.[12] 146-147°.

2- and 4-Bromobenzo[c]cinnoline (4b and 4d).- Hydrazine hydrate (1.6 g, 80%) was added to a mixture of 3a (or of 3b) (2.75 g, 10 mmol) and Raney nickel in hot ethanol (40 ml) with stirring. After refluxing for 1 hr, the hot solution was filtered, and diluted with water; the precipitated product was collected and dried to yield 1.9-2.1 g (73-81%) of 4b which was recrystallized from ethanol, mp. 221-222°, lit.[10] 221-222° ; no mp.

depression was observed with an authentic sample.

Anal. Calcd. for $C_{12}H_7BrN_2$: C, 55.63; H, 2.72; N, 10.81

Found: C, 55.46; H, 2.83; N, 10.76

4d was recrystallized from 2-propanol, 199-200°, lit.[12] 199-200°; no mp. depression was observed with an authentic sample.

3-Bromobenzo[c]cinnoline (4c).- The reaction was carried out using (3.2 g, 10 mmol) of 1a, (8.3 g, 80%) of hydrazine hydrate and Raney nickel in refluxing ethanol and worked up as for 4b, to give 4c. Recrystallization from methanol yielded 2.0 g (77%) of 4c, mp. 194-195°, lit.[12] 194-195°, which had the same spectral characteristics as that described in the literature.[12]

General Procedure for Syntheses of Pyrrolidino, Piperidino, and Morpholinobenzo[c]cinnolines (5-7).- A solution of 4 (0.26 g, 1 mmol) in the amine (10 ml) (pyrrolidine, piperidine, or morpholine) was refluxed (see Table 1); in the reactions of 4a and 4c, dimethyl sulfoxide (5 ml) was added. The excess of amine was evaporated then the residue was diluted with water. The precipitated crude product was collected and the filtrate was extracted with diethyl ether. The etheral solution washed with water, dried over sodium sulfate, and evaporated. The residue was combined with crude product, then chromatographed on a silica gel column (10 g) in dichloromethane-diethyl ether (4:1), and then recrystallized from the solvent(s) that given in Table 1.

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