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PREPARATION OF CINNOLINE-3, 4-DICARBONITRILE AND -DICARBOXYLIC ACID

D. E. AMES* and D. BULL

Chemistry Department, Chelsea College, Manresa Road, London, SW3 6LX, England

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Abstract—Attempts to prepare cinnoline-3,4-dicarboxylic acid from 3,4-dimethylcinnoline failed owing to the unreactivity of the 3-me group. Successive treatment of 3-bromo-4-chlorocinnoline with sodium toluene-*p*-sulphinate and potassium cyanide in dimethylformamide (DMF) gave 4-toluene-*p*-sulphonylcinnoline-3-carbonitrile and then cinnoline-3,4-dicarbonitrile (82%). Hydrolysis yielded cinnoline-3,4-dicarboxylic acid (53%). Cinnoline-3, 4-dicarbonitrile undergoes nucleophilic displacement of either the 4- or the 3-cyano group by ammonia or amine to give 4-amino- and 4-benzylaminocinnoline-3-carbonitrile but 3-dimethylamino-cinnoline-4-carbonitrile.

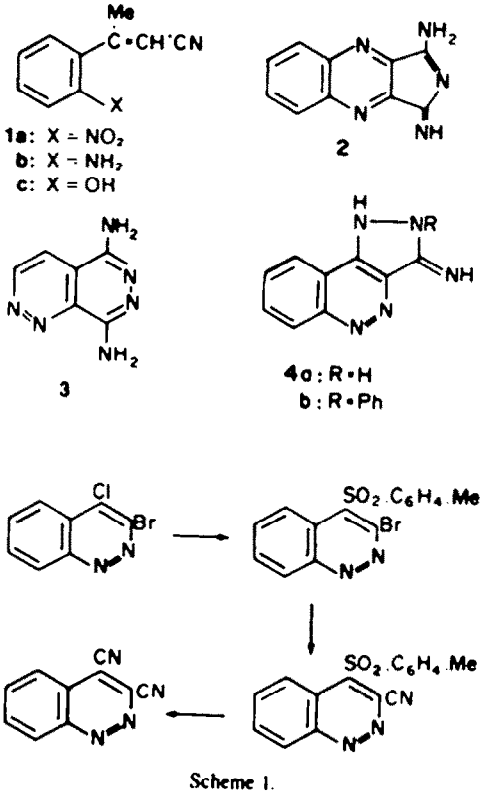
Cinnoline-3,4-dicarbonitrile and -dicarboxylic acid apparently have not been described. The dinitrile has now been prepared in order to examine some of its reactions. We first attempted to obtain the diacid from 3,4-dimethylcinnoline[1] but this approach failed because the 3-me group is very unreactive. Thus oxidation of 3,4-dimethylcinnoline with selenium dioxide gave 3-methylcinnoline-4-carboxaldehyde. Although 4-methylcinnoline was converted into 4-trichloromethylcinnoline by action of sodium hypochlorite solution,[2] 3,4-dimethylcinnoline gave only the 3-methyl-4-aldehyde in low yield. Other halogenating agents also attacked 3,4-dimethylcinnoline only at the 4-substituent: bromine in acetic acid furnished 4-dibromomethyl-3-methylcinnoline and N-chlorosuccinimide yielded 4-chloromethyl-3-methylcinnoline. These results suggested that 4-methylcinnoline-3-carbonitrile would be a useful intermediate for the preparation of the 3,4-dicarboxylic acid. 3-(*o*-Nitrophenyl) but-2-enonitrile (**1a**) was prepared from *o*-nitroacetophenone and diethoxyphosphonoacetonitrile by a modified Wittig reaction.[3] Reduction with iron and water gave 3-(*o*-aminophenyl) but-2-enonitrile (**1b**) but diazotisation then yielded phenol (**1c**) rather than 4-methylcinnoline-3-carbonitrile.

Cinnoline-4-carbonitrile has been prepared from 4-methylsulphonylcinnoline and cyanide ion in DMF[4] or in dimethyl sulphoxide.[5] 3-Bromo-4-chlorocinnoline was condensed with sodium toluene -*p*-sulphinate in DMF at 5° and the intermediate 3-bromo-4-toluene-*p*-sulphonyl cinnoline was treated with excess of potassium cyanide at 5°. Cinnoline-3,4-dicarbonitrile was isolated in 82% yield. When one molar proportion of potassium cyanide was used, 4-toluene-*p*-sulphonylcinnoline-3-carbonitrile was obtained. This was also prepared from 4-chlorocinnoline-3-carbonitrile and sodium toluene-*p*-sulphinate in DMF at 5°. The reaction sequence is thus as shown in the Scheme with the 3-bromo-substituent surprisingly undergoing displacement before the 4-toluene-*p*-sulphonyl group. The two nitriles did not show distinct C≡N bands in the IR spectra but strong bands at about 2240 cm^{-1} were observed in the Raman spectra.

Hydrolysis of cinnoline-3,4-dicarbonitrile with cold, conc.[2] sulphuric acid yielded the diamide whereas heating with hydrochloric acid afforded cinnoline-3,4-dicarboxylic acid (53%).

Rothkopf *et al.*[6] have shown that quinoxaline-2,3-dicarbonitrile reacts with ammonia to give 1-amino-3-imino-3H-pyrrolo-[3,4-b] quinoxaline (**2**). When cinnoline-3,4-dicarbonitrile in methanol containing a trace of copper(II) sulphate was treated with ammonia, however, nucleophilic displacement of the 4-cyano-group occurred to form 4-amino-cinnoline-3-carbonitrile.[7] Similarly the dinitrile reacted with benzylamine in tetrahydrofuran to give 4-benzylaminocinnoline -3-carbonitrile, which was also obtained from benzylamine and 4-chlorocinnoline-3-carbonitrile. In contrast, dimethylamine displaced the 3-cyano group of the dinitrile to form 3-dimethylamino-cinnoline-4-carbonitrile, which was different from the known 4-dimethylaminocinnoline-3-carbonitrile obtained from the 4-chloro compound and dimethylamine. Presumably the secondary amine reacts at the 3-position as there is less steric hindrance to formation of the transition state and intermediate than for 4-substitution.

Nucleophilic displacement of a cyanide group by ammonia or amine has apparently not been reported for



Scheme 1.

other azine or diazine nitriles but 4-cyano-1-methylpyridinium iodide has been shown to give 4-methylamino and 4-hydrazino-1-methylpyridinium salt on reaction with methylamine and hydrazine respectively.[8]

Pyridazino-3,4-dicarbonitrile condenses with hydrazine to form 5,8-diaminopyridazino [4,5–c] pyridazine (3) and related dinitriles behave similarly.[9–11] Treatment of cinnoline-3,4-dicarbonitrile, however, again involved nucleophilic displacement of the 4-cyano group forming 2,3-dihydro-3-imino-1H-pyrazolo [4,3–c] cinnoline (**4a**) previously prepared from 4-chlorocinnoline-3-carbonitrile.[12] Phenylhydrazine similarly gave the corresponding 2-phenyl derivative (**4b**).

EXPERIMENTAL

M.ps (capillary) are uncorrected. NMR spectra were determined at 60 MHz on a Perkin–Elmer R12B spectrometer in DMSO with TMS as internal standard. Mass spectra were determined on an AEI MS-902 spectrometer. Raman spectra were obtained by Dr. A. S. Gilbert (Wellcome Research Laboratories) using a Spex 1301 spectophotometer with argon ion laser excitation.

Oxidation of 3,4-dimethylcinnoline with selenium dioxide (with C. J. A. Byrne)

The cinnoline (2.5 g) and selenium dioxide (4 g) in AcOH (40 ml) were heated under reflux for 4 hr and lead acetate (0.5 g) was added. The mixture was filtered and the filtrate was evaporated to yield a brown oil. Repeated extraction with petrol, evaporation, and crystallisation from petrol gave *3-methylcinnoline-4-carboxaldehyde* (0.7 g; 26%), m.p. 143–145° (Found: C, 69.3; H, 4.7; N, 16.1. $C_{10}H_8N_2O$ requires: C, 69.7; H, 4.7; N, 16.3%), ν_{max} 1690 cm^{-1} (C=O), δ ($CDCl_3$) 3.1 (3H, s, Me), 7.9–8.9 (4H, m, ArH) and 11.1 (1H, s, CHO). When the proportion of selenium dioxide was doubled, the same product was obtained in lower yield (14%).

Action of sodium hypochlorite on methylcinnolines (with Miss B. Pietrzak)

4-Methylcinnoline (1 g) and sodium hypochlorite soln (100 ml; 0.515 M) were stirred under N_2 for 7 days. The solid was collected, washed with water, dried, and extracted with hot benzene-petrol (80–100°) (20 ml; 1:1). Concentration gave *4-trichloromethylcinnoline* (1.32 g; 77%), m.p. 137–138° (Found: C, 43.4; H, 2.2; Cl, 42.7; N, 11.5. $C_9H_5Cl_3N_2$ requires: C, 43.7; H, 2.0; Cl, 43.0; N, 11.3%). Hydrolysis with boiling 4M NaOH, followed by acidification, gave cinnoline-4-carboxylic acid, identical (IR) with an authentic sample.

3,4-Dimethylcinnoline (0.498 g) and sodium hypochlorite soln similarly gave 3-methylcinnoline -4-carboxaldehyde (0.085 g; 16%), m.p. and mixed m.p. 143–145°.

4-Dibromomethyl-3-methylcinnoline

Br_2 (1 ml) in AcOH (5 ml) was added dropwise to a stirred soln of 3,4-dimethylcinnoline (1 g) in AcOH (10 ml). Filtration, and washing with AcOH gave the *product* (1 g; 50%), yellow prisms from EtOH, decomposing above 130° (Found: C, 38.0; H, 2.5; Br, 51.0; N, 8.7. $C_{10}H_8Br_2N_2$ requires: C, 37.9; H, 2.5; Br, 50.6; N, 8.9%), δ 3.1 (3H, s, 3-Me), 7.9 – 8.2 (3H, m, ArH + $CHBr_2$), and 8.5 – 8.9 (2H, m, ArH).

4-Chloromethyl-3-methylcinnoline

3,4-Dimethylcinnoline (1.6 g), N-chlorosuccinimide (2.7 g), benzoyl peroxide (50 mg) and CCl_4 (30 ml) were heated under reflux for 30 min. The solid was filtered off and washed with hot solvent and the combined filtrates were evaporated. Recrystallisations from EtOH gave the *chloro-compound* (0.75 g; 40%), yellow, m.p. 139–140° (Found: C, 62.3; H, 4.5; Cl, 18.4; N, 14.6. $C_{10}H_9ClN_2$ requires: C, 62.3; H, 4.7; N, 14.5%), δ 3.0 (3H, s, 3-Me), 5.3 (2H, s, 4-CH_2Cl), and 7.9 – 8.5 (4H, m, ArH). There is a marked nuclear Overhauser enhancement (approx. 2X) of the 5-H when the CH_2 signal is irradiated with a second radio-frequency signal whereas the CH_3 shows little enhancement. This indicates that the CH_2Cl group is adjacent to the 5-H and must be in the 4-position.

E-3(*o-Nitrophenyl*) *but-2-enonitrile*

Diethoxyphosphonoacetonitrile (8.9 g) in dry 1,2-dimethoxyethane (50 ml) was treated with NaH (1.2 g) in portions over 20 min. The mixture was stirred until all the NaH had reacted and was then treated with *o-nitroacetophenone* (8.5 g) dropwise over 5 min. After 30 min the mixture was evaporated; addition of water and isolation with ether gave the nitrile (6 g; 64%), m.p. 96–97°, from EtOH (Found: C, 63.7; H, 4.5; N, 14.7. $C_{10}H_8N_2O_2$ requires: C, 63.8; H, 4.3; N, 14.9%), ν_{max} 2200 cm^{-1} (CN), δ ($CDCl_3$) 2.4 (3H, d J 0.92 Hz, Me), 5.2 (1H, q, CH) and 7.25 – 8.25 (4H, m, ArH).

E-3(*o-Aminophenyl*) *but-2-enonitrile*

Fe powder (10.75 g) was added in portions to nitro-nitrile (6 g) in water (150 ml) and AcOH (6 ml) and the mixture was refluxed vigorously for 4 hr. The cooled mixture was filtered, the solid being washed repeatedly with EtOAc. Isolation with EtOAc and crystallisation from ether–petrol (60–80°) gave the *amino-nitrile* (4.8 g; 95%), m.p. 68–69° (Found: C, 75.9; H, 6.5; N, 17.7. $C_{10}H_{10}N_2$ requires: C, 75.9; H, 6.4; N, 17.7%), ν_{max} 3380, 3330 (NH_2) and 2200 cm^{-1} (CN); δ ($CDCl_3$) 2.42 (3H, d $J_{H.Me}$ 0.9 Hz, Me), 3.90 (2H, br s, NH_2), 5.57 (1H, q, CH) and 6.6–7.4 (4H, m, ArH).

This amine (2 g) in 2M-HCl (12.5 ml) was diazotised at 0° with $NaNO_2$ (0.9 g) in water (10 ml). The soln was kept at room temp. for 2 days. Isolation with ether and chromatography on silica using heptane–EtOAc (10:1) as solvent yielded E-3(*o-hydroxyphenyl*) *but-2-enonitrile* (0.9 g; 45%), m.p. 59–60° from EtOH. (Found: C, 75.4; H, 5.7; N, 8.8. $C_{10}H_9NO$ requires: C, 75.4; H, 5.7; N, 8.8%) ν_{max} 3350 br (OH) and 2210 cm^{-1} (CN); δ ($CDCl_3$) 2.4 (3H, d $J_{H.Me}$ 0.9 Hz, Me), 6.0 (1H, q, CH), and 6.7 – 7.4 (4H, m, ArH).

Cinnoline-3,4-dicarbonitrile

3-Bromo-4-chlorocinnoline (23.5 g) was dissolved in dry DMF (500 ml) at 0° and treated with dry sodium toluene-*p*-sulphinate (18 g) in one portion. The mixture was stirred vigorously at 0° for 40 min under N_2 and finely-powdered KCN (15.6 g) was added. After the mixture had been stirred at 5–10° for 4 hr, it was left overnight and then poured into ice-water (4 l). Filtration gave a solid which was dissolved in $CHCl_3$; the soln was washed four times with water, treated with charcoal, dried ($MgSO_4$) and evaporated to give *cinnoline-3,4-dicarbonitrile* (14.5 g; 82%), m.p. 185–186° from toluene (Found: C, 66.5; H, 2.3; N, 30.7%; M^+ 180. $C_{10}H_4N_4$ requires: C, 66.7; H, 2.2; N, 31.1% M 180), λ_{max} 254 nm (ϵ, 44500), ν_{max} 2245 cm^{-1} in Raman spectrum (CN).

4-Toluene-p-sulphonylcinnoline-3-carbonitrile

(a) 3-Bromo-4-chlorocinnoline (1.6 g) in dry DMF (30 ml) at 0° was treated with sodium toluene-*p*-sulphinate (1.25 g). The mixture was stirred under N_2 for 40 min and KCN (0.43 g) was added. The mixture was stirred at 10° for 2 hr and left overnight. Addition of ice-water (100 ml), filtration, and crystallisation from toluene gave the *sulphonyl-nitrile* (0.65 g; 33%), m.p. 229–231°. (Found: C, 62.2; H, 3.5; N, 13.3. $C_{16}H_{11}N_3O_2S$ requires: C, 62.1; H, 3.6; N, 13.6%), λ_{max} 252 nm (ϵ, 38000), ν_{max} (IR) 1340 and 1155 cm^{-1} (SO_2) and (Raman) 2235 cm^{-1} (CN), δ ($CDCl_3$) 2.45 (3H, s, Me) and 7.2 – 8.9 (8H, m, ArH).

(b) 4-Chlorocinnoline-3-carbonitrile[12] (0.5 g) in dry DMF was treated at 0° with sodium toluene-*p*-sulphinate (0.5 g) and the mixture was stirred at 5° for 3 hr. Isolation as above gave the sulphonylnitrile, m.p. and mixed m.p. 229–231°.

Cinnoline-3,4-dicarboxylic acid

The dinitrile (2 g) and conc HCl (50 ml) were heated under reflux for 4 hr. The soln was evaporated and the residue was dissolved in 2M NaOH (10 ml) and decolourised with charcoal. Acidification with HCl gave *cinnoline-3,4-dicarboxylic acid hydrate* (1.4 g; 53%), m.p. 178% dec. (Found: C, 50.9; H, 3.3; N, 11.9. $C_{10}H_6N_2O_4.H_2O$ requires: C, 50.9; H, 3.4; N, 11.9%); the

mass spectrum gave M^+ 218 corresponding to the anhyd diacid; ν_{max} 3520 br (OH), 2680–2820 br (COOH) and 1700 cm^{-1} (C=O); λ_{max} 238 and 299 nm (ϵ, 41000 and 4000).

Cinnoline-3,4-dicarboxamide

A soln of cinnoline-3,4-dicarbonitrile (1 g) in conc H_2SO_4 (10 ml) was kept at room temp. overnight and then poured onto ice. Filtration and crystallisation from 2-methoxyethanol gave pale yellow *diamide* (1.2 g) m.p. 340° (sealed tube). (Found: C, 55.2; H, 3.6; N, 26.1%; M^+ 216. $C_{10}H_8N_4O_2$ requires: C, 55.5; H, 3.7; N, 25.9%; M, 216).

4-Aminocinnoline-3-carbonitrile

The dinitrile (0.72 g) was dissolved in THF (12.5 ml) and MeOH (12.5 ml) containing one drop of $CuSO_4$aq. Ammonia was passed through the soln for 30 min. The solid was collected and crystallised from 2-methoxyethanol to give the amino-nitrile (0.4 g; 59%), m.p. above 360° (lit.[7] above 360°) (Found: C, 63.1; H, 3.5; N, 32.7. Calc. for $C_9H_6N_4$: C, 63.5; H, 3.5; N, 32.9%). The same product (IR identical) was obtained by warming 4-chlorocinnoline-3-carbonitrile with ethanolic ammonia, filtering, and crystallising from 3-methoxyethanol.

4-Benzylaminocinnoline-3-carbonitrile

Benzylamine (2.3 ml) was added to a soln of dinitrile (0.25 g) in THF (3 ml) and left overnight. The ppt was collected and crystallised from MeOH to give the *amino-nitrile* (0.26 g; 72%), m.p. 231–232° (Found: C, 73.5; H, 4.5; N, 21.5%; M^+, 260. $C_{16}H_{12}N_4$ requires: C, 73.8; H, 4.6; N, 21.5%; M, 260), ν_{max} 2220 cm^{-1} (CN), δ ($CDCl_3$) 3.18 (1H, s, NH), 5.25 (2H, s, CH_2) and (9H, m, ArH). The same product was obtained by reaction in boiling EtOH but methylamine, ethylamine, and diethylamine, failed to react under either conditions.

3-Dimethylaminocinnoline-4-carbonitrile

Cinnoline-3,4-dicarbonitrile (0.18 g) in THF (3 ml) was treated with ethanolic dimethylamine (2 ml; 33% w/v) and after 2 hr the soln was evaporated. Crystallisation from MeOH gave the *amino-nitrile* (0.12 g; 60%), orange needles, m.p. 138–139°. (Found: C, 66.6; H, 5.3; N, 28.3%; M^+ 198. $C_{11}H_{10}N_4$ requires: C, 66.6; H, 5.1; N, 28.3%; M, 198). ν_{max} 2200 cm^{-1} (CN); δ ($CDCl_3$) 3.6 (6H, s, NMe_2), 7.3 – 8.5 (4H, m, ArH).

4-Dimethylaminocinnoline-3-carbonitrile

4-chlorocinnoline-3- carbonitrile (0.3 g) and dimethylamine in EtOH (5 ml; 33% w/v) were heated under reflux for 10 min. Evaporation and crystallisation from EtOH gave the *product* (0.25 g; 80%), pale yellow needles, m.p. 180–181°. (Found: C, 66.6; H, 4.8; N, 28.4%) which was different from the isomer described. Under the same conditions, benzylamine gave the benzylamino-nitrile described above.

Reaction of cinnoline-3,4-dicarbonitrile with hydrazine

The nitrile (0.1 g) in THF (3 ml) was treated with hydrazine hydrate (0.1 ml) and left overnight. The ppt was collected and crystallised from MeOH-benzene to give 2,3-dihydro-3-imino-1H-pyrazolo [4,3–c] cinnoline, m.p. 325–328°. The product was identical with a sample obtained from 4-chlorocinnoline-3-carbonitrile and hydrazine,[12] the m.p. being 325–328° (lit.[12] 292–293°).

Similarly the dinitrile and phenylhydrazine gave 2,3-dihydro-3-imino-2-phenyl-1H-pyrazolo [4,3–c] cinnoline, m.p. and m.m.p. 236–238° (lit.[12] 236–237°).

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