The Synthesis of Benzofuroquinolines. X. Some Benzofuro[3,2-*c*]isoquinoline Derivatives

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Condensation of salicylonitrile with ethyl α-bromo-α-(*o*-ethoxycarbonylphenyl)acetate (**4**) effectively gave 5(6*H*)-benzofuro[3,2-*c*]isoquinolinone (**2**), which was converted to some 5-substituted benzofuro-[3,2-*c*]isoquinoline derivatives **1a-g**.

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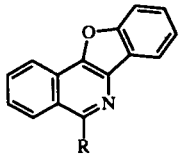
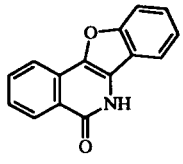
In our course of polycyclic heteroaromatic compounds, we had reported some benzofuroquinolines [1a-d]. Some derivatives of 6(5*H*)-benzofuro[3,2-*c*]quinolinone showed interesting osteogenesis activities [2a,b]. In our previous paper, we reported a preparation of a benzofuroisocoumarin, 5-benzofuro[3,2-*c*][2]benzopyranone (**3**) from methyl salicylate and ethyl α-bromo-α-(*o*-ethoxycarbonylphenyl)acetate (**4**) and its conversion to a new benzofuroisoquinolinone, 5(6*H*)-benzofuro[3,2-*c*]isoquinolinone (**2**) [3]. But, the conversion yield was very low. In this paper, we will describe a new effective preparation of **2** and its conversions to some benzofuro[3,2-*c*]isoquinoline derivatives **1a-g**.



1a R = Cl
1b R = OMe
1c R = CN
1d R = Me
1e R = Bu
1f R = Ts
1g R = $CONH_2$



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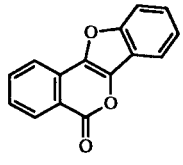

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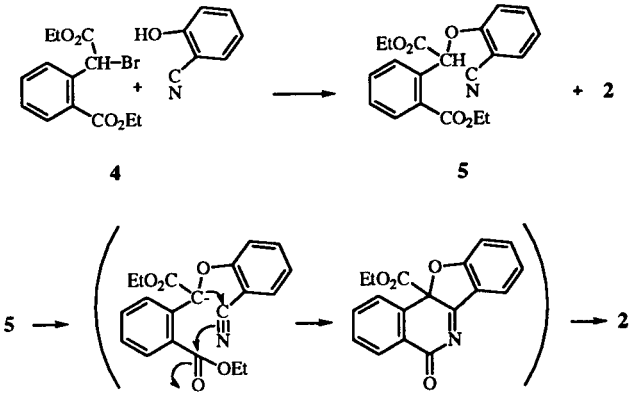
A similar condensation of salicylonitrile with **4** gave a mixture of ethyl α-(*o*-cyanophenyloxy)-α-(*o*-ethoxycarbonylphenyl)acetate (**5**) (65%) and 5(6*H*)-benzofuro-[3,2-*c*]isoquinolinone (**2**) (6%). The cyano ester **5** was readily converted to benzofuroisoquinolinone **2** by a further treatment with sodium hydride in refluxing toluene for 20 hours. This benzofuroisoquinolinone **2** was identical with the sample *via* an ammonolysis of benzofuroisocoumarin **3**, reported previously [3].

Treating benzofuroisoquinolinone **2** with phosphorus pentachloride at 200° effectively gave 5-chlorobenzofuro[3,2-*c*]isoquinoline (**1a**) [4]. This 5-chloro derivative was effectively converted to 5-methoxybenzofuro[3,2-*c*]-isoquinoline (**1b**) and benzofuro[3,2-*c*]isoquinoline-5-carbonitrile (**1c**) by treating with sodium methoxide or copper(I) cyanide [5]. Some conversions of **1a** to unsubstited benzofuro[3,2-*c*]isoquinoline (**1**, R = H) were also attempted by a sodium borohydride reduction, a lithium aluminium hydride reduction, a hydrogenolysis over Pd-C, and metalations followed by hydrolyses. They were all unsuccessful, and **1a** was recovered. Treatment of **1a** with methyllithium or *n*-butyllithium interestingly gave a small amount of 5-methylbenzofuro[3,2-*c*]isoquinoline (**1d**) (19%) or 5-butylbenzofuro[3,2-*c*]isoquinoline (**1e**) (8%), with recovery of large amounts of **1a**. Another conversion of **1a** to unsubstituted benzofuro[3,2-*c*]isoquinoline (**1**, R = H) was also attempted by a thioethylation followed by a hydrogenolysis or a *p*-toluenesulfonhydrazidation followed by an alkaline cleavage. The thioethylation resulted in the recovery of **1a** *p*-toluenesulfonhydrazidation gave 5-(*p*-toluenesulfonyl)benzofuro[3,2-*c*]isoquinoline (**1f**) instead of the 5-tosylhydrazide **1** (R = NHNHTs).

Some conversions of nitrile **1c** to the 5-carboxylic acid derivative **1** (R = CO_2H) were attempted next. Hydrolyses of nitrile **1c** effectively gave benzofuro[3,2-*c*]isoquinoline-5-carbamide (**1f**) by treatment in cold concentrated sulfuric acid at room temperature for 15 days, but further hydrolyses of nitrile **1c** or amide **1g** to the acid were not observed. Another conversion of **1c** to the acid by reduction followed by oxidation was attempted, but reduction with di(isobutyl)aluminium hydride or tin(II) chloride resulted in the recovery of **1c**.



4 **5**

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured on a Hitachi 260-50 spectrophotometer in potassium bromide discs, and the uv spectra were taken on a Hitachi 220A spectrophotometer in ethanolic solutions. The ^1H nmr and ^{13}C nmr spectra were recorded on a JEOL PMX-60Si or FX-90Q NMR spectrometer. The mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer.

Condensation of Salicylonitrile with **4**.

To a solution of salicylonitrile (1.30 g, 10.9 mmoles) and **4** (3.44 g, 10.9 mmoles) [3] in acetone (80 ml) was added anhydrous potassium carbonate (4.54 g, 32.7 mmoles), and the mixture was refluxed for 2 hours. The acetone layer was collected by decantation, concentrated under reduced pressure, and recombined with the solid part. The entire residue was treated with water, acidified with 10% hydrochloric acid, and extracted with ether. The precipitates which were insoluble in both water and ether were collected and recrystallized from ethanol to give 5(6*H*)-benzofuro[3,2-*c*]isoquinolinone **2** (374 mg, 15%), mp 310°; ir: ν CO 1670 cm^{-1}, identical with that of the reported sample [3]. The ether layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the ether gave a crystalline residue, which was recrystallized from benzene-cyclohexane to give ethyl α-(*o*-cyanophenyloxy)-α-(*o*-ethoxycarbonyl-phenyl)acetate (**5**) (2.67 g, 69%), mp 93-94°; ir (potassium bromide): ν CN 2230, ν CO 1750 and 1705 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.2 (t, 3H, J = 7 Hz, Me in CO_2Et), 1.4 (t, 3H, J = 7 Hz, Me in CO_2Et), 4.2 (q, 2H, J = 7 Hz, CH_2 in CO_2Et), 4.4 (q, 2H, J = 7 Hz, CH_2 in CO_2Et), 7.1 (s, 1H, α-CH), 6.9-8.1 ppm (m, 8H, Ar-H); ms: m/z 353 (M^+).

Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.18; H, 5.47; N, 3.95.

Cyclization of **5** to Benzofuroisoquinolinone **2**.

To a solution of **5** (1.15 g, 3.25 mmoles) in dry toluene (40 ml) was added sodium hydride (260 mg, 6.50 mmoles), and the mixture was refluxed for 20 hours. After cooling the mixture was treated with 10% hydrochloric acid. The precipitates were collected and recrystallized from ethanol to give 5(6*H*)-benzofuro[3,2-*c*]isoquinolinone (**2**) (756 mg, 99%).

5-Chlorobenzofuro[3,2-*c*]isoquinoline (**1a**).

A mixture of **2** (1.00 g, 4.25 mmoles) and phosphorus pentachloride (970 mg, 4.68 mmoles) was heated at 200° for 30 minutes. After cooling the mixture was treated with ice-water and extracted with benzene. The benzene layer was washed with saturated sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. Evaporation of the benzene gave a crystalline residue, which was recrystallized from hexane to give 5-chlorobenzofuro[3,2-*c*]isoquinoline (**1a**) (823 mg, 76%), mp 172-173°; ir: ν C-Cl 729 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.3-8.5 (m, Ar-H); ^{13}C nmr (deuteriochloroform): δ 112.1, 120.5, 120.6, 123.6, 123.9, 125.4, 125.5, 127.6, 127.7, 127.9, 131.5, 131.7, 144.3, 146.8, 156.4 ppm; ms: m/z 253 and 255 (M^+); uv (ethanol): 231 (log ε 4.47), 260 (4.49), 287 sh (4.08), 298 (4.18), 309 (4.13), 341 sh (3.92), 354 nm (3.90).

Anal. Calcd. for $C_{15}H_8NOCl$: C, 71.01; H, 3.19; N, 5.52. Found: C, 70.90; H, 3.28; N, 5.49.

5-Methoxybenzofuro[3,2-*c*]isoquinoline (**1b**).

To a methanolic sodium methoxide solution, containing sodium (60 mg, 2.6 mmoles) in methanol (25 ml), was added **1a** (210 mg, 0.828 mmole), and the mixture was refluxed for 47 hours. Evaporation of the methanol gave the crystalline residue, which was diluted with benzene. The benzene layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the benzene gave a crystalline residue, which was recrystallized from ethanol to give 5-methoxybenzofuro[3,2-*c*]isoquinoline (**1b**) (127 mg, 62%), mp 90-91°; ^1H nmr (deuteriochloroform): δ 4.2 (s, 3H, OMe), 7.2-8.4 ppm (m, 8H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 54.1, 112.0, 119.2, 119.8, 120.1, 123.1, 124.9, 125.6, 126.3, 126.4, 130.9, 133.6, 142.2, 156.9, 157.8, 159.2 ppm; ms: m/z 249 (M^+), 220 (M^+ -CHO); uv (ethanol): 229 (log ε 4.48), 250 (4.28), 259 (4.39), 290 sh (4.07), 300 (4.20), 304 (4.20), 310 sh (4.20), 338 (3.99), 350 nm (3.92).

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 76.81; H, 4.49; N, 5.41.

Benzofuro[3,2-*c*]isoquinoline-5-carbonitrile (**1c**).

To a solution of **1a** (1.43 g, 5.64 mmoles) in dry *N,N*-dimethylformamide (60 ml) was added copper(I) cyanide (960 mg, 10.7 mmoles), and the mixture was refluxed for 48 hours. The cooled mixture was poured onto a mixture of water (87 ml) and ethylenediamine (30 ml) and extracted with benzene. The benzene layer was washed with a 10% sodium cyanide solution and then with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the benzene gave a crystalline residue, which was chromatogrammed on a silica-gel column. The fractions eluted with hexane-benzene (1:1) were recrystallized from ethanol to give benzofuro[3,2-*c*]isoquinoline-5-carbonitrile (**1c**) (772 mg, 56%), mp 205-206°; ir: ν CN 2228 cm^{-1}; ms: m/z 244 (M^+); uv (ethanol): 228 (log ε 4.48), 240 sh (4.31), 264 (4.60), 301 (4.03), 314 (3.88), 360 nm (3.92).

Anal. Calcd. for $C_{16}H_8N_2O$: C, 78.68; H, 3.30; N, 11.47. Found: C, 78.39; H, 3.59; N, 11.36.

5-Methylbenzofuro[3,2-*c*]isoquinoline (**1d**).

To a solution of **1a** (216 mg, 0.85 mmole) in dry ether (100 ml) was added 1.6 *M* methyllithium diethyl ether solution (1.60 ml, 2.24 mmoles) by a syringe under an argon atmosphere, and stirred at room temperature for 17 hours. After working up, the ether layer was washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the ether gave a crystalline residue, which was chromatogrammed on a silica-gel column. The fractions eluted with benzene to give **1a** (117 mg, 54%) and 5-methylbenzofuro[3,2-*c*]-isoquinoline (**1d**) (38 mg, 19%). The methyl derivative **1d** was purified by sublimation, mp 135-136°; ^1H nmr (deuteriochloroform): δ 3.12 (s, 3H, Me), 7.4-7.9 (m, 5H, Ar-H), 8.2-8.4 ppm (m, 3H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 22.7, 112.0, 120.4, 120.5, 123.5, 124.2, 125.0, 126.7, 126.8, 126.9, 127.1, 130.6, 139.6, 149.5, 155.0, 156.2 ppm; ms: m/z 233 (M^+); uv: 230 (log ε 4.41), 256 (4.47), 286 (4.04), 295 (4.14), 307 (4.06), 339 (3.82), 349 nm (3.82).

Anal. Calcd. for $C_{16}H_{11}NO+1/2H_2O$: C, 79.31; H, 5.00; N, 5.78. Found: C, 79.60; H, 5.15; N, 5.69.

5-Butylbenzofuro[3,2-*c*]isoquinoline (**1e**).

A similar treatment of **1a** (197 mg, 0.788 mmole) with 1.6 *M*

n-butyllithium-hexane solution (0.74 ml, 1.18 mmoles) gave **1a** (39 mg, 20%) and 5-butylbenzofuro[3,2-*c*]isoquinoline (**1e**) (18 mg, 8%). The butyl derivative was also purified by sublimation, mp 77-80°; ^{1}H nmr (deuteriochloroform): δ 1.1 (t, 3H, Me, J = 6 Hz), 1.3-2.3 (m, 4H, CH_2 x 2), 3.4 (t, 2H, Ar-CH_2-, J = 7 Hz), 7.2-7.9 (m, 5H, Ar-H), 8.1-8.3 (m, 3H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 14.0, 23.1, 32.5, 35.8, 112.0, 120.5, 120.6, 123.4, 124.4, 124.7, 126.0, 126.5, 126.6, 127.0, 130.2, 134.6, 144.0, 156.3, 159.0 ppm; ms: m/z 275 (M^+), 233 (M^+ -C_3H_6).

Anal. Calcd. for $C_{19}H_{17}NO+1/2H_2O$: C, 80.24; H, 6.39; N, 4.93. Found: C, 80.08; H, 6.42; N, 4.83.

Reaction of **1a** with *p*-Toluenesulfonhydrazide.

To a solution of **1a** (630 mg, 2.48 mmoles) in chloroform (100 ml) was added *p*-toluenesulfonhydrazide (2.30 g, 12.4 mmoles), and the mixture was refluxed for 5 days. Evaporation of the chloroform gave the crystalline residue, which was treated with benzene. After removing the insoluble *p*-toluenesulfonhydrazide by filtration, the benzene extracts were chromatographed on a silica-gel column. The fractions eluted with hexane-chloroform (2:3) gave **1a** (309 mg, 49%) and 5-tosylbenzofuro[3,2-*c*]-isoquinoline (**1f**) (167 mg, 18%), mp 212-214°; ir: ν SO_2 1327 and 1155 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 3H, Ar-Me), 7.3-8.1 (m, 6H, Ar-H), 7.3 (d, 2H, Ar-H, J = 8 Hz), 8.1 (d, 2H, Ar-H, J = 8 Hz), 8.4-8.6 (m, 1H, Ar-H), 9.3-9.5 ppm (m, 1H, Ar-H); ms: m/z 373 (M^+), 309 (M^+ -SO_2).

Anal. Calcd. for $C_{22}H_{15}NO_3S$: C, 70.76; H, 4.05; N, 3.75. Found: C, 70.87; H, 4.19; N, 3.84.

Benzofuro[3,2-*c*]isoquinoline-5-carbamide (**1g**).

A mixture of **1c** (48 mg, 0.205 mmole) and concentrated sulfuric acid (10 ml) was stirred at room temperature for 15 days, and then the mixture was poured onto ice-water. The precipitates were collected and recrystallized from ethanol to give benzofuro[3,2-*c*]isoquinoline-5-carbamide (**1g**) (45 mg, 87%), mp 178-180°; ir: ν CO 1632 cm^{-1}; ms: 262 (M^+); uv: 230 (log ε 4.44), 262 (4.43), 285 sh (4.17), 298 sh (4.07), 308 (3.96), 352 nm (3.88).

Anal. Calcd. for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.27; H, 3.82; N, 10.41.

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[3] S. Yamaguchi, Y. Uchiuzoh, and K. Sanada, *J. Heterocyclic Chem.*, **32**, 419 (1995).

[4] Using excess molar phosphorus pentachloride sometimes gave a dichloride, mp 189-191°; ir: ν C-Cl 906 and 743 cm^{-1}; ms: 287, 289, and 291 (M^+).

[5] Using sodium cyanide in DMF was unsuccessful and **1a** was recovered.