A Short Efficient Synthesis of 4-Amino-2,3-dihydrobenzofuran

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A new, practical synthesis of 4-amino-2,3-dihydrobenzofuran is described. Chlorination and a Sandmeyer reaction of the title compound are also reported.

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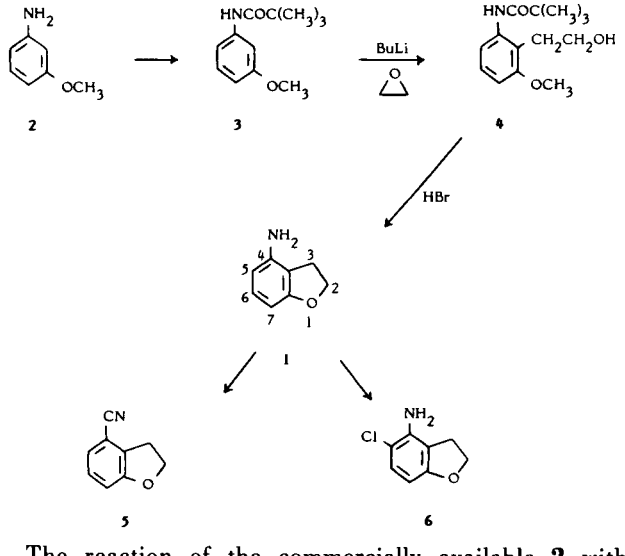
We report in this note a new high yield synthesis of 4-amino-2,3-dihydrobenzofuran (**1**), a compound previously cited in the patent literature (1) but with no accompanying description of its properties. The direct introduction of substituents into position 4 of 2,3-dihydrobenzofuran by electrophilic substitution is highly disfavored and synthesis from 1,2,3-substituted benzene precursors suffers from the unavailability of these starting materials. Thus the synthesis of **1** provides and entry into a series of 4 substituted 2,3-dihydrobenzofurans which we illustrate by conversion of **1** to the 4-cyano derivative (**5**). Entry into the 4,5-disubstituted series is illustrated by the ready preparation of the 4-amino-5-chloro compound (**6**).

The development of this synthesis was prompted by the unsuitability of the previous route which was cumbersome and required the starting material, 6-nitrosalicylaldehyde (2) which is available only with difficulty. Our procedure relies on the elegant work of Fuhrer and Gschwend (3) who described the high yield *ortho* functionalization of *m*-anisidine (**2**) making the route outlined in Scheme I possible.

SCHEME I



The reaction of the commercially available **2** with pivaloyl chloride in pyridine affords **3** in 95% yield (4) while the other two steps, 69% and 70% respectively, give **1** in an overall 46% yield. The 1,2,3 substitution pattern of **4** was defined by proton NMR and its conversion to **1**. The latter was also prepared according to the route outlined (1) and the physical and spectral properties were identical to the material prepared *via* Scheme I. The directed lithiation of **3** has been described (3) and reaction with liquid ethylene oxide posed no problems. Hydrogen bromide catalyzed ether cleavage and cyclization of **4** has a precedent (5) and proceeded smoothly.

A principal utility of **1** lies in its ready conversin to other 4-substituted 2,3-dihydrobenzofurans. Thus, its Sandmeyer chemistry is illustrated by synthesis of the 4-cyano product (**5**) and its electrophilic chemistry by its transformation to **6**, using the chlorination procedure of Neale, *et al.* (6). Since substitution *ortho* (position 5) or *para* (position 7) to the amino group is possible, ^{13}C nmr analysis was required to define the product as the 4-amino-5-chloro product **6**. The proton-coupled ^{13}C nmr data presented in Table I defined the position of substitution as follows: C-5 can be assigned in the unchlorinated material **1** by the fact that it is a doublet (J = 154 Hz) of quartets (J = 6 Hz). This pattern arises from coupling to the C-5 proton and three bond coupling to the NH_2 and C-7 protons. When the NH_2 is exchanged with deuterium oxide a simple doublet of doublets results. In addition, C-7 shows a three bond coupling to the C-5 proton. In the product **6**, C-5 is again assigned by its broad character due to three bond coupling to the NH_2 and the C-7 proton and a two bond coupling to the C-6 H (7). It is now shifted downfield by 5 ppm and no longer shows coupling to a directly bonded H. C-7 becomes a simple doublet (J = 167 Hz) indicating that it is no longer coupled to a proton at C-5. These data are consistent with chlorination at C-5.

EXPERIMENTAL

2-(2'-Hydroxyethyl)-3-methoxypivalanilide (**4**).

To *N*-pivaloylanisidine **3** (4.14 g., 0.02 mole) dissolved in freshly distilled tetrahydrofuran (THF, 60 ml.) and cooled to 0° under an atmosphere of nitrogen, was added 2.3*N* *n*-butyl lithium in hexane (23 ml.). The resultant solution was stirred at 0° for 2 hours. Ethylene oxide (neat, 1.6 ml.) was added. The resulting mixture was stirred for 1 hour at 0° and 1 hour at room temperature and then quenched into water (30 ml.) containing acetic acid (2 ml.). The volatiles were removed by distillation *in vacuo* and the remaining aqueous mixture extracted with ether (2 × 30 ml.).

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Table I

20 MHz ^{13}C NMR Spectra (a)

Assignment Position	Compound 1 c (b)	Multiplicity (a)	(J, Hz)	Compound 6 c (b)	Multiplicity (c)	(J, Hz)
3	27.0	t	(133)	27.8	t	(133)
2	70.3	t	(149)	71.2	t	(150)
7	97.2	d of d	(163, 8)	98.3	d	(167)
5	106.7	d of q	(158) (d)	111.6	m	
3a	109.8	m		108.9	m	
6	128.1	d	(158)	127.9	d	(163)
4	145.3	d	(10)	141.0	d	(8)
7a	160.4	broad d	(9)	159.1	m	

(a) Obtained using a Varian Associates CFT-20 spectrometer, in DMSO-d_6 solution. (b) Decoupled. (c) Fully coupled. (d) On exchange with deuterium oxide a doublet of doublets arises (J = 157, 7 Hz).

The resultant organic phase was separated, washed successively with 5% aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to 5.42 g. of crude crystalline product. Recrystallization from *n*-butyl chloride (13 ml.) afforded 3.46 g. (69%) of 2-(2-hydroxyethyl)-3-methoxypivalanilide **4**, m.p. 118-119.5°; ir (methylene chloride): 2.80μ (OH), 3.05 (NH), 6.01 (CO); nmr (deuteriochloroform): 300 MHz δ 1.28 (s, 9H), 2.42 (t, 1H, OH), 2.86 (t, 2H), 3.80 (s, 3H), 3.89 (m, 2H), 6.89 (dd, 1H, J = 8, 2 Hz, H-4), 7.19 (t, 1H, J = 8.5 Hz, H-5), 7.44 (dd, 1H, J = 8.5, 2 Hz, H-6), 8.95 (broad, 1H, N-H).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.75; H, 8.62; N, 5.29.

Note: On a 0.24 mole scale, it was necessary to add the ethylene oxide liquid at −50° since a vigorous exotherm was noted. After the corresponding aging and workup, a 57% yield of **4**, m.p 117.5-118°, was obtained. An additional 11%, m.p. 112-115°, could be obtained after two additional recrystallizations, one from butyl chloride and one from methylcyclohexane. This material contained a trace (tlc 95% dichloromethane:5% methanol) of starting material but could be carried on to the next step without loss of yield.

4-Amino-2,3-dihydrobenzofuran (**1**).

2-(2'-Hydroxyethyl)-3-methoxypivalanilide, **4** (6.0 g., 0.024 mole) was heated in a sealed tube under nitrogen with 48% hydrobromic acid (60 ml.) for 16 hours at 100°. The solution was then diluted with water (60 ml.) and extracted with ether (2 × 50 ml.). The aqueous solution was concentrated to an oil, redissolved in water (40 ml.) and reevaporated to 6.8 g. of crude product. This, when slurried with acetonitrile (100 ml.) at 0° for 30 minutes, afforded, after filtration, 2.09 g. (41%) of 4-amino-2,3-dihydrobenzofuran hydrobromide, m.p. 254-255°; nmr (deuterium oxide-deuterium chloride): 60 MHz δ 3.37 (t, 2H, J = 8 Hz, CH_2Ar), 4.70 (t, 2H, J = 8 Hz, CH_2O), 7.06 (m, 3H).

Anal. Calcd. for $C_8H_{10}BrNO$: C, 44.44; H, 4.63; N, 6.48; Br, 37.04. Found: C, 44.39; H, 4.49; N, 6.55; Br, 36.91.

The filtrate from the acetonitrile slurry was evaporated to 3 g. of solid which was dissolved in water, cooled, made alkaline with 50% sodium hydroxide and extracted with dichloromethane dried with sodium sulfate and evaporated to 1.5 g. of the free base, a tan oil which is single spot by tlc; ir (dichloromethane): 2.90, 3.0 μ (NH_2) no absorptions below 2.90 (*i.e.* OH) and no CO region absorptions; ms: m/e 135. To the oily free base was added *p*-toluenesulfonic acid monohydrate (2.2 g.) and methanol (5 ml.). The mixture was heated to effect dissolution and then evaporated to dryness. Recrystallization of the residue from acetonitrile (15 ml.) afforded 2.16 g. of the *p*-toluenesulfonate salt of **1**, m.p. 174-175°. The combined yield was 70% (41% as hydrobromide, 29% as *p*-toluenesulfonate).

Anal. Calcd. for $C_{15}H_{17}NO_4S$: C, 58.63; H, 5.54; N, 4.56; S, 10.42. Found: C, 58.69; H, 5.56; N, 4.73; S, 10.43.

Reaction on a 0.135 mole scale gave identical results.

4-Cyano-2,3-dihydrobenzofuran (**5**).

4-Amino-2,3-dihydrobenzofuran (270 mg., 2 mmoles) generated from the hydrobromide by extraction of an alkaline solution with methylene chloride, drying and concentrating was dissolved in 2.5*N* hydrochloric acid (1.75 ml.) and the solution cooled in an ice bath. To this stirred solution was added sodium nitrite (142 mg., 2.05 mmoles) in 0.5 ml. of water. An immediate deep reddish brown color was formed and the presence of excess nitrite was determined by a positive starch-potassium iodide test. The solution was carefully neutralized with solid sodium carbonate. To a stirred heterogeneous mixture of cuprous cyanide (233 mg.) (**8**) and sodium cyanide (196 mg.) in water (2 ml.) and ethyl acetate (4 ml.), cooled in an ice bath, was added the above solution of diazonium salt. The resulting cold solution turned very dark and was stirred for 30 minutes at ice bath temperature and 1 hour at room temperature. The organic phase was separated and the aqueous phase further extracted with more ethyl acetate. The combined organic extracts were washed with water and brine, dried and concentrated to 170 mg. of crude product. Purification by preparative thin layer chromatography (two 1000 μ silica gel plates developed with dichloromethane) afforded a lead band which was eluted to give 60 mg. of 4-cyano-2,3-dihydrobenzofuran; ir: 4.50 μ (CN). A small sample of sublimed *in vacuo* to afford analytical material, m.p. 56.5-57°; nmr (deuteriochloroform): 300 MHz δ 3.43 (t, 2H, J = 8 Hz), 4.71 (t, 2H, J = 8 Hz), 7.03 (d, 1H, J = 6 Hz), 7.17 (d, 1H, J = 6 Hz), 7.27 (t, 1H, J = 6 Hz).

Anal. Calcd. for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.36; H, 4.61; N, 9.73.

4-Amino-5-chloro-2,3-dihydrobenzofuran (**6**).

A mixture of 4-amino-2,3-dihydrobenzofuran (free base, 266 mg., 1.97 mmol and *N*-chlorosuccinimide (270 mg.) in benzene (4 ml.) was refluxed for 2 hours. The benzene was evaporated in a stream of nitrogen and the residue was dissolved in chloroform (7 ml.) and extracted with water (2 × 6 ml.). The organic phase was separated, dried and concentrated to give 305 mg. of the crude product. Purification by sublimation *in vacuo* afforded 251 mg., m.p. 81-82°. Purification by preparative thin layer chromatography of 155 mg. of this material (two 1500 μ silica gel plates, 98% dichloromethane:2% methanol) afforded a lead band which was eluted to 119 mg. (58%) of 4-amino-5-chloro-2,3-dihydrobenzofuran, m.p. 94-95°; ms: parent m/e 169; nmr (deuteriochloroform): 300 MHz δ 3.10 (t, 2H, J = 8.5 Hz), 4.72 (t, 2H, J = 8.5 Hz), 6.20 (d, 1H, J = 8 Hz), 6.96 (d, 1H, J = 8 Hz).

Anal. Calcd. for C_8H_8ClNO: C, 56.64; H, 4.72; N, 8.26; Cl, 20.92. Found: C, 56.29; H, 4.70; N, 8.12; Cl, 20.69.

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