

Synthesis of 3-Aminobenzofuran Derivatives Involving Nitro Displacement

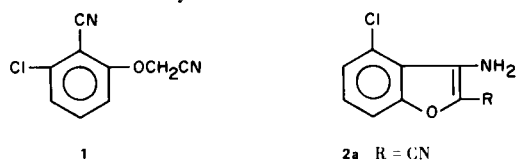
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In a recent paper (1) we described a facile synthesis of methyl 3-aminobenzo[b]thiophene-2-carboxylate esters from *o*-nitrobenzonitriles and methyl thioglycolate. The synthesis involved thioglycolate anion displacement of the nitro function followed by base-catalyzed ring closure. We have now extended this general principle to the preparation of related 3-aminobenzofuran derivatives. Rene and Royer (2) described the synthesis of 2-benzofurancarbonitrile from salicylaldehyde by alkylation with chloroacetonitrile and subsequent base-catalyzed ring closure. Similarly, Pesson and Joannic (3) reported the formation of 3-hydroxy-2-benzofurancarbonitriles by treatment of *o*-(cyanomethoxy) benzoate esters with alkoxides.

When 2-chloro-6-nitrobenzonitrile was allowed to react with glycolonitrile in DMF at room temperature in the presence of lithium hydroxide, the product obtained was 2-chloro-6-(cyanomethoxy)benzonitrile (1) (74% yield). Under the relatively mild conditions used, ring closure to the benzofuran had not occurred. However, treatment of 1 with potassium carbonate in DMF at 100° did yield 3-amino-4-chloro-2-benzofurancarbonitrile (2a) (50%). When potassium hydroxide in refluxing alcohol was used, the product obtained from 1 was 3-amino-4-chloro-2-benzofurancarboxamide (2b) (70%). Attempted ring closure with sodium methoxide in refluxing methanol gave the imino ether 2c (49%). This type of synthesis allows the preparation of 3-amino-2-benzofurancarbonitriles and carboxamides from readily available *o*-nitrobenzonitriles.



EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. 2-Chloro-6-nitrobenzonitrile (Aldrich Chemical Co.) and glycolonitrile (70% technical, Matheson, Coleman and Bell) were available commercially.

2-Chloro-6-(cyanomethoxy)benzonitrile (1).

To a solution containing 5.5 g. of 2-chloro-6-nitrobenzonitrile (30.1 mmoles) and 5 ml. of glycolonitrile (70% technical) in 60 ml. of DMF was added portionwise 1.0 g. of lithium hydroxide. The mixture was stirred for 2 hours and then poured into ice water. The crude product was collected and crystallized from alcohol-water to yield 4.3 (74%) of product, m.p. 126-127.5°; nmr

(deuteriochloroform): δ 4.92 (s, 2, OCH₂CN).

Anal. Calcd. for C₉H₅ClN₂O: C, 56.12; H, 2.62; N, 14.54. Found: C, 55.92; H, 2.53; N, 14.33.

3-Amino-4-chloro-2-benzofurancarbonitrile (2a).

A solution containing 3.4 g. of 1 (17.7 mmoles) and 2.0 g. of anhydrous potassium carbonate in 50 ml. of DMF was heated at steam-bath temperature for 7 hours and then poured into ice water. The crude product was collected and crystallized from benzene-Skellysolve B to yield 1.7 g. (50%) of product, m.p. 159-160°; nmr (deuteriochloroform): δ 4.80 (broad, 2, exchangeable, amino); ir (chloroform): 2200 cm⁻¹ (nitrile), 3360 and 3480 cm⁻¹ (amino); uv λ max (alcohol): 239 nm (ϵ , 16,980), 297 nm (ϵ , 9,630), 313 nm (ϵ , 10,030).

Anal. Calcd. for C₉H₅ClN₂O: C, 56.12; H, 2.62; N, 14.54. Found: C, 56.30; H, 2.76; N, 14.65.

3-Amino-4-chloro-2-benzofurancarboxamide (2b).

A mixture containing 3.5 g. of 1 (18.2 mmoles) and 1.0 g. of potassium hydroxide in 40 ml. of alcohol was refluxed for 2 hours. The product, m.p. 194.5-196°, crystallized from the cooled reaction mixture and the yield was 2.7 g. (70%). Recrystallization from benzene gave an analytical sample, m.p. 196-198°; nmr (DMSO-d₆): δ 5.80 (broad, 2, exchangeable, amino), 7.40 (broad, 2, exchangeable, CONH₂); ir (Nujol): 1685, 3160, 3360, and 3490 cm⁻¹; uv λ max (alcohol): 245 nm (ϵ , 11,990), 299 nm (ϵ , 7,750), 319 nm (ϵ , 9,500).

Anal. Calcd. for C₉H₇ClN₂O₂: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.33; H, 3.30; N, 13.20.

Methyl 3-Amino-4-chlorobenzofuran-2-carboximidate (2c).

A solution containing 3.9 g. of 1 (20.2 mmoles) and 1.3 g. of sodium methoxide (24 mmoles) in 60 ml. of methanol was refluxed for 2 hours. Water (20 ml.) was added and the mixture was cooled to yield 2.2 g. (49%) of product, m.p. 147-148°, nmr (deuteriochloroform): δ 4.00 (s, 3, OCH₃), 4.80 (broad, 2, exchangeable, amino), 7.65 (broad, 1, exchangeable, imine); ir (Nujol): 3320, 3400, and 3500 cm⁻¹; uv λ max (alcohol): 246 nm (ϵ , 13,790), 302 nm (ϵ , 11,910), 316 nm (ϵ , 13,550).

Anal. Calcd. for C₁₀H₉ClN₂O₂: C, 53.47; H, 4.04; N, 12.47. Found: C, 53.62; H, 4.22; N, 12.50.

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