

Note

Synthesis of 2-amino-5-chlorobenzonitrile

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Synthesis of 2-amino-5-chlorobenzonitrile by using cheaper and easily available raw materials is discussed.

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Aromatic nitriles have a wide range of applications in pharmaceutical, pesticide and dye industries¹. Aromatic nitriles are used in the manufacture of protective coatings, moulding resins, antioxidants and optical brighteners¹. They are important intermediates for the synthesis of pharmacologically important compounds like neuroleptics, sedatives, tranquillizers, muscle relaxants, etc. Substituted benzonitriles are used for the synthesis of neuroleptic benzodiazepine derivatives such as loflazepate², chlorazepate³, tetrazepam⁴ and climazolam⁵. The compound, 2-amino-5-chlorobenzonitrile, is not easily available in India. Hence, study of its synthesis has a considerable significance.

Results and Discussion

Synthesis of 2-amino-5-chlorobenzonitrile is reported in the literature by two methods. The first method⁶ involves synthesis from 2-aminobenzonitrile, N-chlorosuccinimide and acetonitrile. The second method⁷ involves synthesis from 5-chloroisatin- β -oxime and bis(2-ethylhexyl)phthalate. Both the methods are not feasible commercially as far as the cost and availability of raw materials are concerned.

The route followed for the synthesis of 2-amino-5-chlorobenzonitrile in the laboratory was based on the common and simple reactions (**Scheme I**). The synthetic route involved four steps. In step 1, ring chlorination of anthranilic acid was carried out using sulphonyl chloride so as to get 5-chloroanthranilic acid. This acid was then converted to the corres-

ponding acid chloride by reacting it with thionyl chloride. Amination of the acid chloride with liquor ammonia produced 2-amino-5-chlorobenzamide. The amide thus formed was finally dehydrated using a powerful dehydrating agent, P₂O₅, to get 2-amino-5-chlorobenzonitrile. No stringent conditions were required to be maintained during the reactions. Handling and storage of chemicals were quite safe and the yield of 2-amino-5-chlorobenzonitrile was also satisfactory.

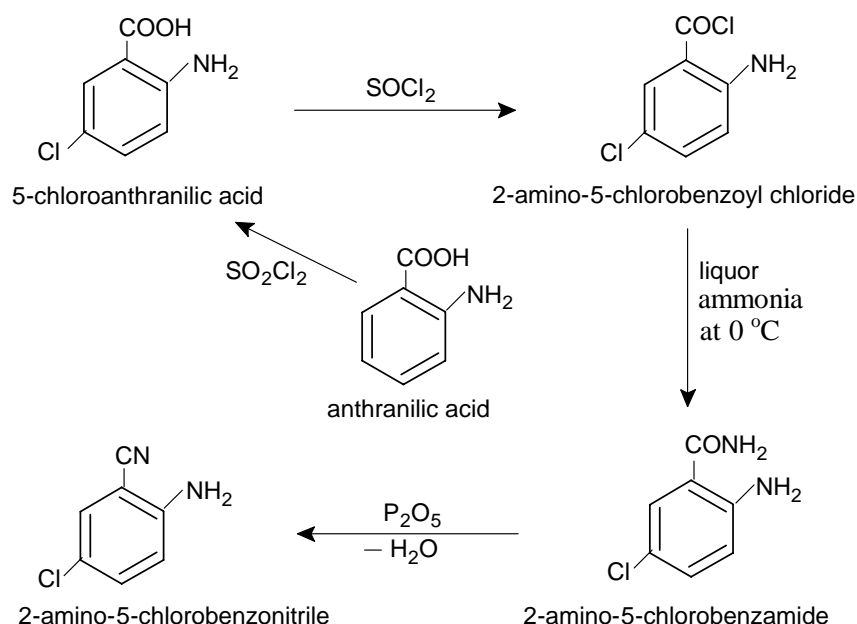
Experimental Section

Melting points of the synthesized compounds are uncorrected. IR spectra in KBr were recorded on a JASCO FTIR 410 spectrometer; ¹H NMR spectrum at 90 MHz in CDCl₃ on a Varian-EM-390 ¹H NMR spectrometer (chemical shifts in δ , ppm) using TMS as internal standard; and mass spectrum on a quadrupole mass spectrometer by the Electron Impact (EI) method.

A safe, economically feasible and hence a promising route for the synthesis of 2-amino-5-chlorobenzonitrile was based on the use of anthranilic acid (**Scheme I**). The method involved four steps as follows:

(i) **Ring chlorination of anthranilic acid by using sulphonyl chloride**⁸. Anthranilic acid (2 g, 15 mmoles) was added in small portions, during 10 min, to the solution of sulphonyl chloride (2.6 g, 19 mmoles) in anhydrous ether (35 mL), taken in a round bottom flask. Excess sulphonyl chloride was removed by vacuum distillation. The residue was refluxed with 8% hydrochloric acid (40 mL) at 60-70 °C for 1¹/₂ hr. The solution was filtered and the precipitate of 5-chloroanthranilic acid was obtained by adding sodium acetate to the filtrate. It was washed with cold water and recrystallized from 1:1 aqueous ethanol to get the pure product, m.p. 203-04°C, yield 35%; R_f 0.49; IR (KBr): 3556, 3468 (N-H str, 1° amine), 1672 (C=O str), 1611 (N-H ben), 1599, 1564, 1471, 1448 (C=C str, Ar), 1311 (O=C-O⁻ str, carboxylate anion), 610 cm⁻¹ (C-Cl str).

(ii) **Conversion of 5-chloroanthranilic acid to 2-amino-5-chlorobenzoyl chloride by using thionyl chloride**. A mixture of thionyl chloride (1.18 g, 69



mmoles) and 5-chloroanthranilic acid (1 g, 6 mmoles) was taken in a round bottom flask. The reaction mixture was refluxed for 30 min in a water-bath and then filtered. The product was washed with cold water and dried. It was recrystallized from benzene, m.p. 120-21 °C, yield 37%; R_f : 0.90; IR (KBr): 3468, 3358 (N-H str, 1° amine), 1670 (C=O str), 1611 (N-H ben), 1589, 1576, 1508, 1474 (C=C str, Ar), 760 cm^{-1} (C-Cl str).

(iii) Conversion of 2-amino-5-chlorobenzoyl chloride to 2-amino-5-chlorobenzamide by using liquor ammonia. Liquor ammonia (10 mL, 25%) was taken in a round bottom flask and was cooled in an ice-bath to maintain the temperature at 0°C. To this cold liquor ammonia, 2-amino-5-chlorobenzoyl chloride (1 g, 5 mmoles) was added and the flask was shaken frequently for 30 min. The reaction mixture was filtered and the precipitate was washed with water and dried. The product was recrystallized with hot water, m.p. 170-71°C, yield 68%; R_f : 0.71; IR (KBr): 3546, 3401, 3169 (N-H str, 1° amine and amide), 1678 (C=O str), 1617 (N-H ben), 1584, 1549, 1508, 1482 (C=C str, Ar), 1311 (O=C-O⁻ str, carboxylate anion), 610 cm^{-1} (C-Cl str).

(iv) Dehydration of 2-amino-5-chlorobenzamide by using phosphorus pentoxide. Phosphorus pentoxide (2 g, 14 mmoles) and 2-amino-5-chlorobenzamide (1 g, 6 mmoles) were taken in a round bottom flask. The reaction mixture was shaken for 30 min and then vacuum distilled for 1 hr. The distillate

containing 2-amino-5-chlorobenzonitrile and phosphoric acid was collected. It was filtered off to separate the solid product, 2-amino-5-chlorobenzonitrile, from phosphoric acid. It was washed with cold water and recrystallized from aqueous ethanol (60:40), m.p. 96-97°C; yield 63%; R_f : 0.77; IR (KBr): 3405, 3340 (N-H str, 1° amine), 2220 (C≡N str), 1645 (N-H ben), 1599, 1564, 1471, 1448 (C=C str, Ar), 610 cm^{-1} (C-Cl str); ¹H NMR (CDCl₃): δ 7.2 (s, 1H, ArH), 6.72 (d, $J = 9.0$ Hz, 1H, ArH), 6.60 (d, $J = 9.0$ Hz, 1H, Ar), 5.2 (s, 2H, NH₂); Mass: m/z (%) 152 (M⁺) (100), 153 (8.8), 154 (30.9), 124 (5.0), 125 (30.0), 126 (5.0), 127 (10.0), 118 (15.0), 117 (10.0), 90 (30.0), 77 (10.0), 63 (25.0), 53 (15.0), 37, 38, 39 (15.0). Anal. Calcd for C₇H₅N₂Cl: C, 54.90; H, 3.53; N, 18.30, Cl, 23.20. Found: C, 54.83; H, 3.62; N, 18.28, Cl, 23.16%.

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