

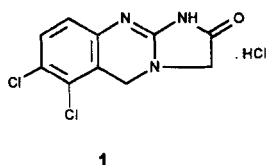
A Simple Synthesis of 2,3-Dichloro-6-nitrobenzonitrile

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Anagrelide (1) [1–2] is in development as a new drug to be used in essential thrombocythemia [3–4], heart disease and stroke [5] in America and Europe [6–7]. It has a strong blood platelet aggregation inhibitory activity without reducing the count of platelets [8] based on the selective blocking of c-AMP PDE and thus reducing the concentration of c-AMP in blood platelets [9–11].



Anagrelide

One of the key intermediates of its synthesis is 2,3-dichloro-6-nitrobenzonitrile (4) which was synthesized first by Dutch authors [12] by the reaction of 2,3,4-trichloronitro-benzene (3) with copper (I) cyanide in pyridine at 170 °C. The melt obtained after the reaction was acidified with hydrochloric acid, extracted with benzene, the benzene layer was evaporated to dryness and triturated with ligroine to yield 59% of crude product that had to be recrystallised from ethanol. The greatest drawback of this method is that hydrogen cyanide is liberated from the unreacted copper (I) cyanide during the work up of the melt with hydrochloric acid, and that the copper (I) chloride formed is insoluble in the black reaction mixture creating problems for its extraction with benzene at large scale.

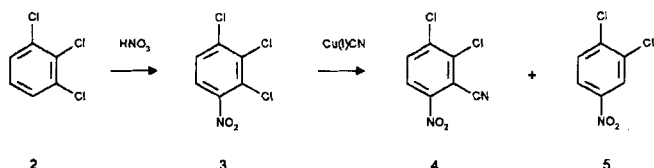
The above method was improved by E. F. Elsager and coworkers [13] by performing the reaction in *N*-methylpyrrolidone at 145–150 °C for 6 hours followed by stirring the reaction mixture at room temperature for 18 hours. The black reaction mixture obtained was then poured with stirring into the 35 fold amount water and stirred until the black tarry material containing also the mixture of copper (I) chloride and

hydroxide salts solidified. The solid was filtered off, washed thoroughly with water, air dried, extracted with the 27 fold amount of boiling ethanol, filtered, the filtrate decolourized with charcoal, filtered again and evaporated *in vacuo* to dryness to yield 59% of crude product that had to be recrystallised from ethanol. This method is again not applicable in industrial scale according to its extremely large volume requirements and the problems of the solidification of the black tarry oils.

We have investigated the above methods in detail by GC and observed that in reactions run either in pyridine or *N*-methylpyrrolidone at 150 °C through long reaction time (6 hours) a serious amount (about 30%) of by-products was formed. From among the by-products the predominant compound was 1,2-dichloro-4-nitrobenzene (5) formed in different runs in 5–15% yield. To get rid of the above by-products we tried to shorten the reaction time by increasing the reaction temperature. However, the use of the above solvents led to the formation of different dimeric by-products as proved by GC-MS [(EI): $M^+ = 336$ (4 Cl), 358 (4 Cl), 369 (4 Cl)].

The solution of the above problem was obtained by using *N,N*-dimethylformamide in rather small quantities (less than 1 fold!) as the solvent, maintaining the temperature of the exothermal reaction between 170–175 °C while enabling short reaction times (30 min). This method led to the reaction mixtures containing less than 12% of by-products (GC). However, the problem of the work up of the reaction mixture still remained, because ill-defined copper (I) salts crystallised together with the product. This problem was solved by addition of an aqueous solution of ferric chloride to the reaction mixture that oxidized the copper (I) salts to copper (II) ones, soluble in water, thereby enabling simple filtration of the product from the reaction mixture in a relatively pure form that after recrystallisation from 2-propanol gave 68% of pure 2,3-dichloro-6-nitrobenzonitrile (4).

The above method is applicable to large scales and gives satisfactory results with raw 4-nitro-1,2,3-trichlorobenzene prepared from 1,2,3-trichlorobenzene (2) by the method described in the Experimental Part. The above procedure was patented recently [14].



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Experimental

The GC investigations were performed with a Shimadzu GC-9a instrument and a Chrompack, CP-SIL-PCB 25 m long semicapillary column, detector FID. The GC-MS measurements were performed with a Carlo Erba HRGC/MS instrument and the same column as in GC. The HPLC investigations were done using a KNAUER apparatus (KNAUER HPLC PUMP 64, KNAUER absorbance detector MODEL UV-1, column: KNAUER C-8; different mixtures of acetonitrile and 0.1 M ammonium acetate buffer, pH = 4.4 were used as eluents). Calibration was made with the use of pure samples.

4-Nitro-1,2,3-trichlorobenzene (3)

Nitric acid (100 %, 1130 ml, 1710 g) was dropped with stirring into nitric acid (65%, 480 ml, 620 g) to yield 33.0 moles of 90% nitric acid. Then 1,2,3-trichlorobenzene (2) (1000 g, 5.3 mol) (Fluka, HPLC purity: 99.2–99.5 %, *o*-dichlorobenzene content 0.4–0.7%) was added at a rate to keep the reaction temperature between 25–30 °C. After the addition was complete the reaction mixture was stirred at 35 °C for 1 hour. After cooling to room temperature the mixture was diluted with dichloromethane (1000 ml) and poured into crushed ice (3 kg). The phases were separated, the aqueous phase was extracted with dichloromethane (2×500 ml), the combined organic layers were extracted with water (500 ml) and saturated sodium chloride solution (500 ml) and dried over anhydrous magnesium sulfate and evaporated *in vacuo* to dryness to yield 1205 g (98.1%) of 3, *m.p.* 52–55 °C [Lit. [2] *m.p.* 52–54.5 °C] [HPLC content: 98.0% of 3, 1.1% of 5-nitro-1,2,3-trichlorobenzene, 0.5% of 1,2,3-trichlorobenzene (2) and 0.2 % of 1,2-dichloro-4-nitrobenzene (5)].

2,3-Dichloro-6-nitrobenzonitrile (4)

To a solution of 3 (940 g, 4 mol) in *N,N*-dimethylformamide (550 ml) preheated to 140 °C, copper (I) cyanide (360 g, 4 mol) was added, and the mixture was heated with stirring at 170 °C for 1 hour. After cooling to 90 °C, 33% ferric chloride solution (2 litres) was added to the reaction mixture during about 5 min. The mixture obtained was stirred for 1 hour, charcoal (20 g) was added, and the crystals precipitated were filtered off to yield 970 g of crude 2,3-dichloro-6-nitrobenzonitrile (4) [GC composition: 88.5% of 4, 5.9% of 1,2-dichloro-4-nitrobenzene (5), 3.2% of 3, 0.6% of 2-chloro-6-

nitro-1,3-benzodinitrile, 0.4% of 2,3-dichloro-6-nitro-benzoic acid amide, 0.2% of 5-nitro-1,2,3-trichlorobenzene]. The crude product was recrystallised from 2-propanol (1800 ml, 25 g of charcoal), and the charcoal was filtered off from the hot solution to yield after cooling 594 g (68.4%) of pure 4, *m.p.* 90.0–91.5 °C (Lit. [5] *m.p.* 90–93 °C), (HPLC purity: 98.3%).

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