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ONE POT SYNTHESIS OF 2,6-DICHLORO-3,5-DICYANOPYRIDINE FROM ALIPHATIC PRECURSORS

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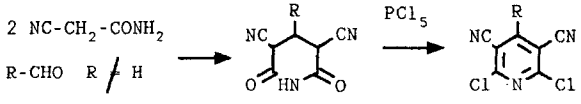
Abstract Malononitrile is condensed with triethyl orthoformate in the presence of pyridine; the mixture is acidified with HCl gas and after addition of further pyridine.HCl diazotised to form 2,6-dichloro-3,5-dicyanopyridine in a convenient, high yield process.

INTRODUCTION

We needed multigram quantities of 2,6-dichloro-3,5-dicyanopyridine (**DCDCP**) as a multifunctional building block for the synthesis of monomers and polymers. DCDCP is mentioned once in the literature as an "also of course possible" product in a patent[1] discussing 4-substituted analogs. We first tried essentially the classical Guareschi[2] method - i.e. condensing cyanoacetamide with an aldehyde, cyclizing to the six



Guareschi approach

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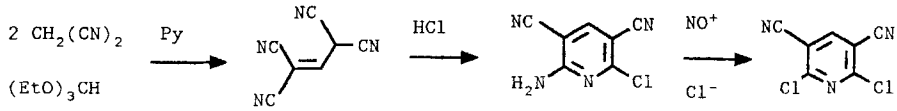
membered imide and treating the imide with PCl_5. All our efforts along this approach (involving formaldehyde or formaldehyde generators) were in vain. Using chloroform rather than formaldehyde to generate dicyanopyridinediol upon cyclization did furnish the pyridinediol, but we could not substitute the oxygen functionality by chlorine with PCl_5, $POCl_3$, its combinations, or related reagents. The method detailed in Ref. 1 belongs in this group and proved fruitless. Switching to a different chemistry, to wit, cyclization of dinitrile to an aminopyridine followed by diazotization at a very high chloride ion concentration proved successful as a low-cost convenient (one-pot) method to prepare sizable quantities of DCDCP. In addition to its potential as a monomer (to react with bis-nucleophiles such as diamines) or a monomer building block, DCDCP may be of interest as a precursor for multidentate ligands by reductive coupling of the pyridyl chloride moiety, notably by the process described by Colon.[3]

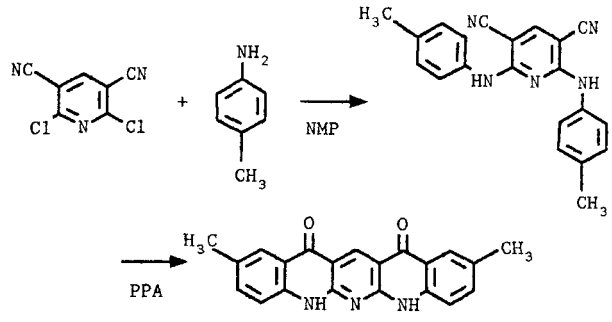
RESULTS

Cyclization of the condensate of malononitrile with triethyl orthoformate by acidifying the condensation mixture, to produce 2-amino-6-chloro-3,5-dicyanopyridine **1** has been described[4] and this process gave no problems in our hands. Chlorinative deamination of **1** by treatment with nitrosylsulfuric acid in molten pyridinium chloride resulted in clean formation of DCDCP. Such a molten chloride at near neutral pH seemed an economical means to increase the likelihood of chloride ion reacting as a nucleophile,[5] compared with using excess of CuCl or for example alkali halide with crown ether. From the outset, we reasoned that this approach should be amenable to integration into a one-pot procedure. We were delighted to find out that the nitrosyl sulfuric acid (which in small scale operations is relatively expensive) could be substituted by strongly acidified sodium nitrite and that indeed the system: melt condensation with pyridine activator, acidification with HCl gas followed by addition of more pyridinium



chloride and a mixture of sodium nitrite and sulfuric acid resulted in clean formation of DCDCP.

The two chlorine atoms can be differentially substituted provided the first substitution is done with a relatively weak nucleophile, such as an aromatic amine. With aliphatic amines it proved difficult (at temperatures > 0 °C) to avoid isolating diaminopyridine



derivatives as the main products. As an example of the further elaborations one can envision with DCDCP, we describe the coupling plus cyclization with p-toluidine.

In **conclusion**, 4-unsubstituted 2,6-dichloro-3,5-dicyanopyridine will now be easily available and its multifunctional character promises a varied range of uses.

EXPERIMENTAL

Commercial laboratory grade starting materials were used without further purification.

2,6-Dichloro-3,5-dicyanopyridine, DCDCP. 60.00 g of malononitrile (908 mmol), 67.32 g of triethyl orthoformate (454 mmol) and 36 g of pyridine are refluxed for 30 min. 150 ml of acetic acid is added and 90 g of HCl gas is passed through in 4 h at 80 °C. The reflux condenser is exchanged for a distillation set-up and in 30 min the excess HCl and the ethanol formed are evaporated. Then the mixture is cooled, a further 96 ml of acetic acid and 240.0 g of pyridine.HCl is added. In a separate flask, 220.8 g (3.2 mol) of sodium nitrite is slurried in 96 ml of acetic acid; 360 g of concentrated sulfuric acid is added in small portions to the bluish white slurry with cooling; some nitrous fumes are produced. The organic reaction mixture is added slowly, with stirring to the nitrous acid mixture at room temperature; the combined mass quickly becomes clear and nitrogen is evolved. After two hours the mixture is warmed to 50 °C for 1 h; then 2 l of water with ice are slowly added, the product

crystallizes and is filtered off, washed with water and dried at 40 °C, 1 mbar for 16 h: Yield 36.9 g (41 % overall), mp 210 - 214.5 °C (15 K/min) with sublimation starting at about 170 °C. IR (KBr, transmission): 3060, 2250, 1587, 1528, 1414, 1395; weak bands at 1243, 1224, 1215, 1210, 1173, 1152; 1130, 1027 (w), 988, 948, 749, 702, 514 (w), 407 (w) cm^{-1}. ^1H NMR ($CDCl_3$): 8.27 ppm (s, 1H). ^{13}C NMR ($CDCl_3$): 110.5 (C-CN), 112.5 (CN), 147.0 (CH), 154.0 (C-Cl) ppm from TMS. MS: M^+ 197, secondary peaks M + 2 199; M - 35 162.

Coupling product with p-toluidine, 2,6-bis(4-methylphenylamino)-3,5-dicyanopyridine. 2.000 g of 2,6-dichloro-3,5-dicyanopyridine (10.10 mmol) and 2.1645 g of p-toluidine (20.20 mmol) are dissolved in 40 ml of NMP. An exothermic reaction is noted. After 10 min, 2.8 ml of 1-ethylpiperidine is added to the yellow turbid mixture: this turns into a clear, red solution as it is further heated to 120 °C. After 2 h at 120 °C the mixture is cooled somewhat, excess water is added, the precipitate is filtered off, washed with water and dried (100 °C, 1 mbar, 18 h). Yield is 94 % of pure product infusible. IR (DRIFT, Kubelka-Munk): 3298, 2212, 1617, 1592, 1523, 1429, 1337 (w), 1214 (w), 812, 757 (w), 501 (w) cm^{-1}. ^1H NMR (99 % D_2SO_4, $DHSO_4$ fixed at 12.00 ppm): 2.92 (s, 6 H - toluidine methyl), 7.48 (d, 2 Hz, 4 H - toluidine C-H ortho vs NH), 7.70 (d, 2 Hz, 4 H - toluidine C-H meta vs NH), 9.24 ppm (s, 1 H, pyridine C-H) ppm. No carbon NMR was recorded due to the low solubility of this compound.

Cyclized product, 2,10-dimethyl-12,14-dioxodibenz[b,i]anthyridine. 1.0 g of the above coupling product is mixed with 35 g of polyphosphoric acid (84+ % of P_2O_5) and heated to 200 °C. Dissolution of the starting material proceeds slowly: at first an orange slurry is produced, which changes colour to deep red in about 15 min and takes about 90 min to become clear. The clear solution is poured into excess water while still hot; the precipitate is filtered off, washed with water and dried. The red infusible product turns deep brownish green when exposed to base. IR (DRIFT, Kubelka-Munk): Broad intense band 3700-2000, peaking at 3000; 1640, 1590, 1454, 1244, 1217, 1075, 1002, 896, 823, 789, 515 cm^{-1} (red form). ^1H NMR (99 % D_2SO_4, $DHSO_4$ fixed at 12.00 ppm): 3.18 (s, 6 H, methyl), 8.36 (d, 2.1 Hz, 2 H, H-4; 8), 8.65 (d, 2.1 Hz, 2 H, H-3; 9), 8.74 (s, 2 H, H-1; 11), 10.71 (s, 1 H, H-13) ppm. No carbon NMR was recorded due to the low solubility of this compound.

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