Synthesis of 2,2′-Bipyrimidine Derivatives

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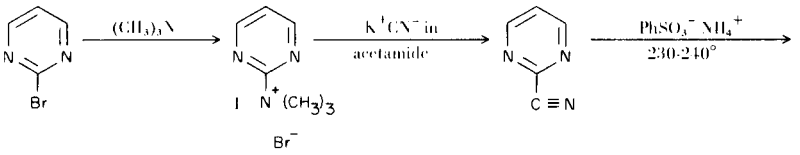
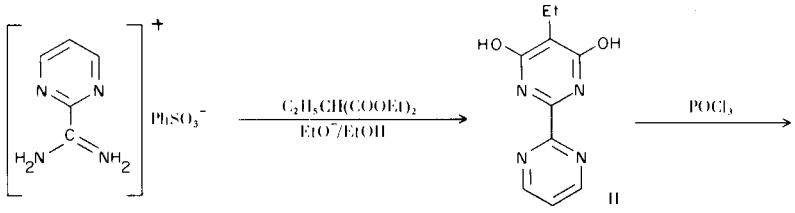
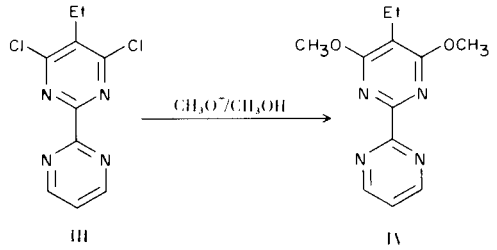
A new total synthesis of 2,2′-bipyrimidine derivatives by the direct condensation of 2-amidinopyrimidinebenzenesulfonate with dicarbonyl compounds is described. The following 2,2′-bipyrimidines have been prepared: 5-ethyl-4,6-dihydroxy-2,2′-bipyrimidine; 5-ethyl-4,6-dichloro-2,2′-bipyrimidine; 4,6-dihydroxy-2,2′-bipyrimidine; 5-ethyl-4,6-dimethoxy-2,2′-bipyrimidine.

Diazines are known to yield polymeric complexes wtih some transition metal ions, having a composition of diazine:metal of 1:1 (1-4). An investigation is being carried out in this laboratory dealing with structural, and some physical, properties of transition metal complexes of substituted pyrimidines (5). Since we were interested in studying in this connection, the transition metal complexes of the 2,2′-bipyrimidine system, attempts were made to synthesize some of its derivatives.

Only a few bipyrimidines have been reported in the literature (6). These were made mainly by using the Ulmann (7) and the Busch (8) biaryl synthesis and by the condensation of amidines with β-dicarbonyl compounds (9). The Ulmann reaction was used to prepare some of







the simple bipyrimidines, 2,2′-bipyrimidine (10), some bis-substituted 2,2′-bipyrimidines (11,12), 4,4′-bipyrimidines (13) and 5,5′-bipyrimidines, (6,14). Some bis-substituted bipyrimidines such as 2,2′,6,6′-tetramethyl-4,4′-bipyrimidine and 2,2′-dimethyl-5,5′-bipyrimidine (6) were prepared under the conditions of the Busch reaction. 4,4′-Bipyrimidine was prepared (7% yield) by the pyrolysis of the copper (II) salt of pyrimidine-4-carboxylic acid (12).

The condensation of amidines with β-dicarbonyl compounds has been a principal method for pyrimidine synthesis (9). Various 2-(2-pyridyl)pyrimidines have been prepared by condensing picolinamidines with β-dicarbonyl compounds (12). Unsuccessful attempts were made to prepare 2,2′-bipyrimidine systems by reacting benzenesulfonates of 2-amidinopyrimidines with ethyl acetoacetate under similar conditions (7). The first reported example of the preparation of a bipyrimidine system by such a condensation was that of 4-hydroxy-6,6′-dimethyl-2,2′-diphenyl-2,4′-bipyrimidine (7).

Low yields of 2,2′-bipyrimidine were obtained using the Ulmann reaction, in which 2-bromopyrimidine was treated with copper in DMF (10). Applying this method to the synthesis of 2,2′-bipyrimidine derivatives having substituents on one ring only (in which we were interested) is not advantageous, since it might result in a mixture of three different coupling products. Consequently, a total synthesis of substituted 2,2′-bipyrimidine systems had to be developed. This was achieved by the condensation of 2-amidinopyrimidinebenzenesulfonate with β-dicarbonyl compounds such as diethyl ethylmalonate.

The method employed to synthesize the 2,2′-bipyrimidine derivatives is outlined in Scheme I.

The 2-amidinopyrimidinebenzenesulfonate was prepared by heating the ammonium salt of benzenesulfonic acid with 2-cyanopyrimidine at 230-240° (7,15). 2-Cyanopyrimidine was prepared by allowing 2-pyrimidine-trimethylammonium bromide to react with potassium cyanide in acetamide (16). The yield of the 2,2′-bipyrimidine derivative (II) obtained in the condensation step was 40%. 4,6-Dihydroxy-2,2′-bipyrimidine was similarly prepared by condensing 2-amidinopyrimidinebenzenesulfonate with diethyl malonate.

EXPERIMENTAL

2-Pyrimidinetrimethylammonium Bromide (I).

The method used for preparing the corresponding chloride was applied (17). 2-Bromopyrimidine (15 g., 0.093 mole) was added to a stirred solution of trimethylamine (15 g.) in benzene. The quaternary salt (20.4 g., 96%) was precipitated. This was used without further purification for the synthesis of the 2-cyanopyrimidine (16).

5-Ethyl-4,6-dihydroxy-2,2′-bipyrimidine (II).

A solution of sodium ethoxide in ethanol was prepared by adding sodium (8 g., 0.35 mole) to absolute ethanol under anhydrous conditions. Diethyl ethylmalonate (32 g., 0.17 mole) was added to this solution. This was followed by addition, in portions, of 2-amidinopyrimidinebenzenesulfonate (7,15) (46 g., 0.165 mole). The reaction mixture was stirred for 24 hours at room temperature and filtered, and the solid residue was washed with ethanol. Water was then added to the ethanolic filtrate and the precipitate which formed was collected and combined with the solid residue. This solid was then suspended in hot water (100 ml.), acidified with hydrochloric acid to *p*H 2, and cooled with ice. The yellow crystals which precipitated were collected and recrystallized from ethanol, yield 14.5 g., 40%, m.p. 259-260°; nmr: 1.23 ppm (t, J = 6.00-6.75 cps, 3H); 2.76 ppm (q, J = 6.00-6.75 cps, 2H); 8.10 ppm (t, J = 5.25-6.00 cps, 1H); 9.30 ppm (d, J = 5.25-6.00 cps, 2H).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.05; H, 4.62; N, 25.47. Found: C, 54.88; H, 4.81; N, 25.21.

5-Ethyl-4,6-dichloro-2,2′-bipyrimidine (III).

5-Ethyl-4,6-dihydroxy-2,2′-bipyrimidine (10 g., 0.045 mole) was refluxed with phosphoryl chloride (60 ml.) for one hour during which time the reaction mixture changed to a clear, colored solution. Excess phosphoryl chloride was evaporated in a vacuum, and the residue was poured onto ice (250 g.) and made basic by adding sodium hydroxide solution (20%). The precipitate formed was collected and recrystallized from ethanol (4.8 g., 41%), m.p. 182-183°; nmr: 1.27 ppm (t, J = 7.5 cps, 3H); 3.01 ppm (q, J = 7.5 cps, 2H); 7.40 ppm (t, J = 5.25 cps, 1H); 8.97 ppm (d, J = 5.25 cps, 2H).

Anal. Calcd. for $C_{10}H_8Cl_2N_4$: C, 47.09; H, 3.16; N, 21.95; Cl, 27.80. Found: C, 47.11; H, 3.28; N, 22.10; Cl, 27.39.

5-Ethyl-4,6-dimethoxy-2,2′-bipyrimidine (IV).

The dichloro derivative (III) (1 g., 0.004 mole) was added to a solution of sodium (0.4 g., 0.0175 mole) in methanol (50 ml.). The mixture was refluxed for 2 hours, cooled to room temperature and filtered. The filtrate was then evaporated, and the residue was extracted with ether. The ethereal solution was dried and evaporated to dryness, and the residue recrystallized from petroleum ether (80-100°), 0.82 g., 85% of IV were obtained, m.p. 103-105°; nmr: 1.10 ppm (t, J = 7.5 cps, 3H); 2.55 ppm (q, J = 7.5 cps, 2H); 4.05 ppm (s, 6H); 7.20 ppm (t, J = 5.25 cps, 1H); 8.75 ppm (d, J = 5.25 cps, 2H).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.74. Found: C, 58.10; H, 5.81; N, 22.43.

4,6-Dihydroxy-2,2′-bipyrimidine (V).

Diethyl malonate (3.2 g., 0.02 mole) was added to a solution of sodium ethoxide in absolute ethanol (1 g., of sodium in 60 ml. of ethanol) under anhydrous conditions. This was followed by addition, in portions, of 2-amidinopyrimidinebenzenesulfonate (5.6 g., 0.02 mole) which gave a yellow precipitate. The reaction mixture was stirred overnight at room temperature and the precipitate was collected. More precipitate was recovered from the filtrate by addition of water. The combined precipitates were dissolved in a small volume of water. Hydrochloric acid (1:1) was added to this aqueous solution (to *p*H 4-5). A precipitate formed on cooling, which was recrystallized from ethanol (1.5 g., 40%), m.p. 261°; nmr: 6.50 ppm (s, 1H); 8.18 ppm (t, J = 7.5-8.0 cps, 1H); 9.52 ppm (d, J = 7.5-8.0 cps, 2H).

Anal. Calcd. for $C_8H_6N_4O_2$: C, 50.34; H, 3.18; N, 29.45. Found: C, 50.18; H, 3.32; N, 29.23.

Nuclear Magnetic Resonance.

Nmr spectra were recorded on a JEOL 60 MHz spectrometer, employing 5-10% concentrations in deuteriochloroform and trifluoroacetic acid (for compound II). All chemical shifts are given in ppm from internal TMS.

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