Synthesis of 2,2′-Bipyrimidine from 2-Bromopyrimidine

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Of the many simple pyrimidine derivatives, only two contain a halogen substituted exclusively in the 2-position. These are 2-chloropyrimidine and 2-fluoropyrimidine.[2-6] The chloro derivative is an important intermediate in the synthesis of certain biologically active compounds,[5] by serving as a route to a quaternary amine salt. As might be expected, however, it will not form a Grignard compound,[7,8] nor will it undergo an Ullman reaction.[7,8]

In contrast, 2-bromopyrimidine, the synthesis of which is included here, can be made to undergo the Ullman reaction without difficulty. It will also form the quaternary amine salt from trimethyl amine at a much more rapid rate than 2-chloropyrimidine and do so in 97–100% yield.

The best yields of 2-bromopyrimidine obtained in this work were by a reverse addition diazotization of the amine in the presence of a bromide salt. Kogon, Minin, and Overberger[4] were able to convert 2-aminopyrimidine to 2-chloropyrimidine by diazotization in concentrated hydrochloric acid, but their method failed when applied by us to the preparation of 2-bromopyrimidine because the predominant reaction was that of hydrobromic acid with nitrous acid to produce bromine, nitric oxide, and water. However, by keeping the concentration of hydrobromic acid at a minimum, by reverse addition, this undesirable reaction was nearly completely avoided. It is interesting to note that, in this "reverse addition" method, replacement of the amine by halogen occurs in a very weakly acidic media, contrary to the suggestion that a high concentration of strong acid is necessary.[5,6] It now appears that the concentration of the anion is the controlling factor. Upon realizing this, it was tested and found that 2-chloropyrimidine, as well as 2-bromopyrimidine, could be prepared by the reverse addition diazotization method in weak acid, and that this could be done with yields comparable to those obtained by Kogon, Minin, and Overberger.

Since it is known that phosphorus oxybromide will replace the hydroxyl group with bromine in pyridazinols[9] and pyrazinols[10] in nearly quantitative yield, it appeared that the action of phosphorus oxybromide on 2-pyrimidinol would be a good route to 2-bromopyrimidine. This turned out not to be the case, however, as the best yields were in the 8–10% range. The low yield is evidently due to the fact that a large portion of the 2-pyrimidinol exists in the ketonic form. This form is not brominated, and the rate of conversion between forms is slow under these conditions.

Applications of the method of Brown[11] to the preparation of 2-pyrimidinol resulted repeatedly in failure. Extensive decomposition of the product occurred in the neutralization and drying steps. The details of the work-up procedure are most important and several revisions were necessitated, for example, the use of drying under reduced pressure at room temperature.

So far as these authors can determine, the Ullman reaction on 2-bromopyrimidine is the first on a halo pyrimidine, and it has resulted in the first direct synthesis of a bipyrimidine. The compound, 2,2′-bipyrimidine, and some of its substituted derivatives which are in early development stages in this laboratory, has long been wanted for studies for analytical purposes. The symmetrically opposing N–C–C–N linkage is thus far unique.

The ultraviolet spectrum of 2-bromopyrimidine, as determined on a Cary Model 10–11 spectrophotometer, was unaffected by pH in the range 2 to 10. At λ_{max} 255 mμ, log a_m = 3.37. This was also true in the case of 2-chloropyrimidine, where λ_{max} was 250 mμ, and log a_m = 3.42. The spectra of 2-pyrimidinol and 2-aminopyrimidine did vary with pH in this range, as reported in the literature.[11] The spectrum of 2,2′-bipyrimidine in distilled water had a λ_{max} of 241 mμ and log a_m 4.20. An unexpected shoulder, occurring at longer wave lengths, in an acidic solution of 2,2′-bipyrimidine is being investigated along with the use of this compound as a reagent for the estimation of iron in acidic solution.

Experimental[12]

Preparation of 2-Bromopyrimidine. I. By Reverse Addition Diazotization.—Into a 500-ml., three-necked flask, equipped with a stirrer, dropping funnel, and thermometer, were added 80 ml. of water, 90 g. of sodium bromide, 30 g. (0.428 mole) of sodium nitrite, and 20 g. (0.214 mole) of 2-aminopyrimidine. After the mixture was cooled to −10°, 48 ml. (0.428 mole) of concentrated hydrobromic acid was

(1) Taken in part from the Ph.D. thesis of D. D. Bly, Purdue University (1962).

(2) D. J. Brown, *Rev. Pure Appl. Chem.*, **3**, 155 (1953).

(3) G. W. Kenner and A. Todd, in Elderfield "Heterocyclic Compounds," Vol. VI, Wiley, New York, N. Y., 1957, pp. 234–323.

(4) I. C. Kogon, R. Minin, and C. G. Overberger, *Org. Syn.*, **35**, 34 (1955).

(5) Kenneth L. Howard (to American Cyanamid Co.), U.S. Patent 2,477,409, July 26, 1949 [*Chem. Abstr.*, **43**, 8105f (1949)].

(6) D. E. Weisbach, M.S. thesis, University of North Carolina (1954). Claim is made to the synthesis of 2-fluoropyrimidine, but the method has evidently not been published.

(7) M. L. Moss, Ph.D. thesis, Purdue University (1942).

(8) E. C. Copelin, Ph.D. thesis, Purdue University (1958).

(9) C. Grundman, *Chem. Ber.*, **81**, 7 (1948).

(10) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **78**, 2141 (1956).

(11) D. J. Brown, *Nature*, **165**, 1010 (1950).

(12) All melting points uncorrected. The infrared spectra of all the pyrimidines, determined on a Perkin-Elmer Model 221 instrument with sodium chloride optics, were consistent with proposed structures.

added dropwise over a period of 3 hr., since the heat of reaction is high and the temperature range must be kept at −3 to −10°. Then an additional reaction time of 1 hr. was allowed, after which air was blown through the solution to remove bromine and oxides of nitrogen.

The solution was made strongly alkaline with cold 40% sodium hydroxide, filtered with suction and the filtrate and residue each extracted with four 100-ml. portions of carbon tetrachloride. The extracts were combined and allowed to evaporate dry at room temperature. The yield of crude 2-bromopyrimidine was 9.1 g. (0.057 mole, 26.6%). A double crystallization from purified petroleum ether (b.p. 60–70°) yielded 7.2 g. of white crystals, m.p. 55.50–57.0°.

Anal. Calcd. for $C_4H_3BrN_2$: C, 30.2; H, 1.9; Br, 50.4; N, 17.6. Found: C, 30.14; H, 2.11; Br, 50.68; N, 17.45.

II. Use of Phosphorus Oxybromide.[13]—A 6.0-g. portion (0.06 mole) of 2-pyrimidinol was brought to boil with 140 ml. of toluene, and 10 ml. was distilled to remove any moisture present. Then 40 g. (0.14 mole) of purified liquid phosphorus oxybromide at 80° was introduced. After heating the mixture at reflux for 1.75 hr., it was placed in an ice bath, cooled to 40°, and 50 ml. of ice water was added over a period of 10 min. with shaking. The aqueous layer was separated, the toluene extracted with 20 ml. of dilute hydrobromic acid and the aqueous layers combined.

The solution was made strongly alkaline with 40% sodium hydroxide at a temperature below 50°. This solution was then extracted with four 50-ml. portions of carbon tetrachloride, which were combined and allowed to evaporate to dryness at room temperature. The yield of crude 2-bromopyrimidine, 0.7 g., was taken up in 150 ml. of boiling petroleum ether (b.p. 60–70°). This was cooled to 0°, filtered to remove phosphorus-containing impurities, evaporated to 30 ml., cooled again to 0°, and filtered to yield 0.5 g. (5%) of white crystalline 2-bromopyrimidine, m.p. 56-57.5°.

Anal. Calcd. for $C_4H_3BrN_2$: C, 30.2; H, 1.9; Br, 50.4; N, 17.6. Found: C, 30.6; H, 2.1; Br, 49.5; N, 17.2.

Synthesis of 2,2′-Bipyrimidine.—All glassware was oven-dried at 140°. Into a 300-ml. flask, fitted with a stirrer, reflux condenser (protected with a calcium chloride tube), and nitrogen inlet were added 30 g. of activated Natural Copper Fine 44-F, 20 g. (0.126 mole) of 2-bromopyrimidine, and 100 ml. of dimethylformamide (distilled from calcium hydride). The mixture was purged with nitrogen for 10 min. with stirring, the nitrogen inlet was then replaced with a thermometer, and the solution brought rapidly to reflux by a mantel. After 3.5 hr., 5 g. of activated copper was added to the gently refluxing solution. Stirring was maintained at all times. At the end of 8 hr., the mixture was cooled to 10° and filtered through coarse paper with suction.[14] The copper residue was placed in a large beaker and extracted for 2 min. by stirring in a 200-ml. solution of concentrated ammonium hydroxide to which had been added 40 g. of potassium cyanide. The mixture was separated by suction filtration, and the extraction then repeated on the residue with a fresh ammonical potassium cyanide solution. To the combined filtrates was added 2 g. of potassium cyanide. This solution was then extracted with four 200-ml. portions of chloroform. The chloroform was placed in an evaporating dish and evaporated in a high velocity hood.[15]

Enough ethyl acetate was added to the tarry, semicrystalline residue to dissolve it, then a few milliliters excess. A small amount of carbon black (Darco) was added and the mixture was held at reflux for 15 min. The hot mixture was filtered. Then enough hot petroleum ether (b.p. 90–100°) was added to the ethyl acetate solution until a slight permanent cloudiness occurred at 80°. This mixture was slowly cooled to 0° with stirring, and filtered again to yield 5.1 g. of tan crystalline solid. The purification steps were repeated to give 3.5 g. (0.022 mole), 35% theory, of white crystalline 2,2′-bipyrimidine, m.p. 113.0–115.0° after vacuum drying. (In other runs, the yield varied from 10 to 50%.)

Anal. Calcd. for $C_8H_6N_4$: C, 60.7; H, 3.82; N, 35.5. Found: C, 60.40; H, 3.53; N, 35.41.

Molecular weight, determined in distilled water by a Mechrolab osmometer, Model 301A, was 306, indicating a dimer; in benzene it was 160, indicating the monomer.

Preparation of 2-Chloropyrimidine by Reverse Addition Diazotization.—This procedure was the same as for 2-bromopyrimidine except that sodium chloride and hydrochloric acid were substituted for sodium bromide and hydrobromic acid, respectively. It is important not to let the temperature get and stay below −10°, as an efficient salt–ice bath might tend to do in this case.

Preparation of 2-Pyrimidinol.—A 30-g. portion of 2-aminopyrimidine was refluxed for 16 hr. in 200 ml. of 10 *M* sodium hydroxide with two clay plate chips keeping the phases mixed. The mixture was cooled to 0°, whipped to a "cream," and filtered on paper with suction. The solid sodium oxypyrimidine was scraped into a large beaker, placed in an ice bath on a magnetic stirrer, and slowly acidified to pH 3.7 by stirring in dilute ice-cold sulfuric acid. Removal of the solvent was begun immediately at room temperature by slowly reducing the pressure to 5 mm. All attempts to remove the water by evaporation on a steam plate, as proposed by Brown, led to decomposition and loss of product. When the solids appeared rather dry from the outside, they were removed, crushed, and further dried at 0.5 mm. and 50° until the hydrates began to release their water and spatter around in the flask. After crushing the solids again, an additional 0.5 hr. of drying was required to remove all of the water of hydration. This was necessary to prevent decomposition during the extraction step.

The dry solid was then refluxed for 30 min. each with three 2-l. increments of dry ethyl acetate. Each increment was decanted through paper, cooled to 0°, and filtered again to obtain the white crystals. The filtrate was saved for future use as it still contained 0.5 g. of 2-pyrimidinol per liter.

The 2-pyrimidinol obtained by several repetitions of the above procedure was consistently pure, m.p. 178–179° (lit., 178–179°[11]) with yields of 21–27 g., 65–90%. Ultraviolet spectra agreed with those of Brown.[11]

(13) The phosphorus oxybromide was supplied with the compliments of the Great Lakes Chemical Corporation. It was purified by distillation, b.p. 60–65°/5–7 mm., and by crystallization, m.p. 56–60°, from 60–70° petroleum ether.

(14) This filtration is slow, but it is necessary to wait until all of the dimethylformamide is removed from the copper bipyrimidine complex; otherwise it interferes in subsequent steps. This solvent is used for the reaction because of its solvent power and because its boiling point lies below the decomposition temperature of 2-bromopyrimidine, but above that necessary to initiate the reaction.

(15) The chloroform forms a stable complex with the 2,2′-bipyrimidine. Evaporation of the last 50 ml. or so is very slow. Azeotropic distillation with portions of carbon tetrachloride may also be used. In both cases some 2,2′-bipyrimidine is lost with the solvent in evaporation.

The Preparation of Furan-2,5-dicarboxylic Acid[1]

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Although dehydromucic acid (furan-2,5-dicarboxylic acid) has been known since before 1900,