Chemistry of Heterocyclic Compounds, Vol. 37, No. 2, 2001

INVESTIGATIONS OF IMIDAZOLES. 101*. SYNTHESIS OF 2,3-DIHYDROIMIDAZO-[1,2-*a*]PYRIMIDINE FROM 2-AMINOPYRIMIDINE

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Two novel preparative methods have been developed for the synthesis of 2,3-dihydroimidazo[1,2-a]-pyrimidine from 2-aminopyrimidine. These are the reaction with 1,2-dibromoethane and also the reaction with ethylene chloro(bromo)hydrin, subsequent treatment of 1-β-hydroxyethyl-2-imino-1,2-dihydropyrimidine with thionyl chloride, and cyclization of the intermediate 1-β-chloroethyl-2-imino-1,2-dihydropyrimidine in the presence of sodium hydroxide.

Keywords: 2-aminopyrimidine, 1,2-dibromoethane, dihydroimidazopyrimidine, imidazole, ethylene chloro(bromo)hydrin, cyclization.

The synthesis is known for 2,3-dihydroimidazo[1,2-*a*]pyrimidine [2] and certain of its derivatives substituted in the pyrimidine part of the molecule [3, 4] from 2-methylmercaptopyrimidine [2] and from 2-chloropyrimidine and its C-substituted derivatives. A drawback of these synthetic methods for imidazolinopyrimidine and its derivatives is the difficulty in obtaining the starting materials and also the need for carrying out the reaction at high temperature (180°C when using 2-methylmercaptopyrimidine) [2].

We have developed two simpler methods for preparing 2,3-dihydroimidazo[1,2-*a*]pyrimidine which is based on the use of 2-aminopyrimidine (available as an intermediate in the production of the sulfanilamide preparation sulfadiazine).

In the first of these methods 2-aminopyrimidine is heated with ethylene chlorohydrin or ethylene bromohydrin in an organic solvent to give 1-β-hydroxyethyl-2-imino-1,2-dihydropyrimidine hydrochloride or hydrobromide **1a,b**.

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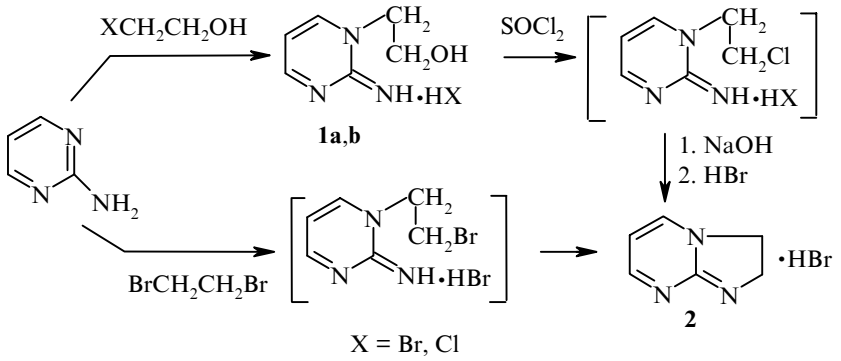
 0009-3122/01/3702-0224$25.00



Upon treatment with thionyl chloride, compounds **1a,b** are converted to 1-β-chloroethyl-2-imino-1,2-dihydropyrimidine. Without separation of the pure material, the latter is heated with sodium hydroxide in ethanol. Separation of a molecule of hydrogen chloride then occurs to form 2,3-dihydroimidazo[1,2-*a*]-pyrimidine (**2**) which is isolated as the hydrobromide in 93% yield. Compound **2** has been reported previously as the hydrochloride [2].

A still simpler, single stage method for the synthesis of the bicyclic compound **2** involves the reaction of 2-aminopyrimidine with 1,2-dibromoethane by heating in a mixture of DMF and butanol. The yield of compound **2** is 90%.

EXPERIMENTAL

The purity of the compounds obtained was determined using TLC on Silufol UV-254 plates and visualization with iodine vapor or UV light.

1-β-Hydroxyethyl-2-imino-1,2-dihydropyrimidine Hydrochloride (1a). A solution of 2-aminopyrimidine (1.9 g, 0.02 mol) and ethylene chlorohydrin (3.2 g, 0.04 mol) in anhydrous toluene (8 ml) was refluxed for 8 h. The solvent was decanted and the residue was triturated with acetone, and the precipitate was filtered, washed with acetone, and dried to give compound **1a** (2.7 g, 77%) as colorless crystals; mp 178-180°C (decomp., from ethanol). Found, %: C 41.30; H 5.50; Cl 19.80; N 23.90. $C_6H_9N_3O·HCl$. Calculated, %: C 41.00; H 5.70; Cl 20.20; N 23.90.

1-β-Hydroxyethyl-2-imino-1,2-dihydropyrimidine Hydrobromide (1b). A solution of 2-aminopyrimidine (9.5 g, 0.1 mol) and ethylene bromohydrin (9.0 g, 0.11 mol) in a mixture of butanol (40 ml) and DMF (10 ml) was refluxed for 9 h, cooled, and the precipitate was filtered off, washed with ether, and dried to give compound **1b** (17.6 g, 80%) as colorless crystals; mp 183-185°C (decomp., from propan-2-ol). Found, %: C 35.20; H 5.10; Br 39.40; N 20.80. $C_6H_9N_3O·HBr$. Calculated, %: C 35.30; H 5.10; Br 39.20; N 20.60.

2,3-Dihydroimidazo[1,2-*a*]pyrimidine Hydrobromide (2). A. Thionyl chloride (8-10 ml) was added carefully to compound **1a** or **1b** (0.01 mol). The mixture was refluxed for 2 h, thionyl chloride distilled in vacuo to dryness, a 10% alcoholic solution of sodium hydroxide (40 ml) was added, and the product was refluxed for 2 h. The solvent was distilled off in vacuo, the residue extracted with acetone with heating (2 × 20 ml), the solution filtered, and 42-46% hydrobromic acid (1 ml) was added. The precipitate was filtered, washed with ether, and dried to give compound **2** (2.0 g, 93%) as colorless prisms; mp 281-283°C (decomp., from butanol). Found, %: C 38.90; H 3.80; Br 37.20; N 19.30. $C_6H_7N_3·HBr$. Calculated, %: C 39.30; H 3.80; Br 37.30; N 19.60.

B. A solution of 2-aminopyrimidine (2.9 g, 0.03 mol) and 1,2-dibromoethane (16.9 g, 0.09 mol) in a mixture of DMF (5 ml) and butanol (15 ml) was refluxed for 6 h, cooled, and the precipitate was filtered off, washed with ether, and dried to give compound **2** (5.8 g, 90%); mp 281-283°C (decomp., from butanol). A sample mixed with a sample of compound **2** prepared by method A did not show a depression of melting point.

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