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SYNTHESIS OF 4-CHLORO-1,2,3-TRIAZOLE DERIVATIVES BY DIAZOTIZATION OF 6-SUBSTITUTED 5-AMINO-4-CHLOROPYRIMIDINES

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It is shown that 4-cyano- and 4-carbalkoxy-5-chloro-1,2,3-triazoles, respectively, are formed in the diazotization of 4,6-dichloro- and 4-chloro-6-alkoxy-5-aminopyrimidines. It was observed that a methyl group in the 2 position of the starting pyrimidine derivative does not affect the structures of the reaction products under the described conditions.

Despite the extensive use of reactions involving the transformation of heterocyclic systems in synthetic organic chemistry [1], they occupy an insignificant position among the methods for the preparation of 1,2,3-triazole derivatives [2]. In particular, the conversion of 5-diazouracils to 1,2,3-triazoles was reported only in 1976 [3].

We have previously shown that sulfides of 4-methoxy-5-amino-6-mercaptopyrimidine are converted by diazotization to methyl 1,2,3-triazole-4-carboxylate derivatives [4]. In a continuation of this research we studied the behavior of 6-substituted 5-amino-4-chloropyrimidines under similar conditions.

It is known that the structures of the products of diazotization of 5-aminopyrimidines depend on the character of the substituents in the pyrimidine ring [5]. The substituents in the 2, 4, or 6 position of the 5-aminopyrimidine molecule often undergo various transformations during diazotization. For example, 2,4-dichloro-5-aminopyrimidine forms a diazouracil [6]. 4,6-Dichloro-5-aminopyrimidine (Ia) and its 6-substituted derivatives such as 6-alkoxy-5-amino-4-chloropyrimidines, which are converted by diazotization to 4-chloro-1,2,3-triazole-5-carboxylic acid derivatives, behave differently. Thus treatment of 4,6-dichloro-5-aminopyrimidine with sodium nitrite in aqueous HCl leads to the production of 4-chloro-5-cyano-1,2,3-triazole (IIa), whereas 5-carbomethoxy- and 5-carbethoxy-4-chloro-1,2,3-triazoles (IIb, c) are formed from 4-methoxy- and 4-ethoxy-5-amino-6-chloropyrimidines (Ib, c), respectively.

With respect to both its melting point and its spectral characteristics, IIc corresponds to the 4-chloro-5-carbethoxy-1,2,3-triazole recently obtained by other methods [7, 8] (see the experimental section).

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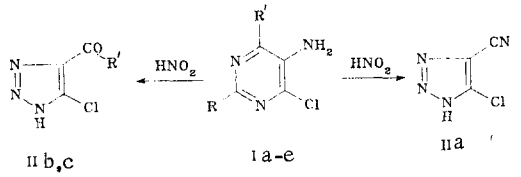

IIb,c Ia-e IIa

I a R=H, R′=Cl; b R=H, R′=OCH_3; c R=H, R′=OC_2H_5; d R=CH_3, R′=Cl; e R=CH_3, R′=OCH_3; II b R′=OCH_3, c R′=OC_2H_5

The formation of 1,2,3-triazole derivatives in the diazotization of 5-aminopyrimidines evidently includes as one of the first steps the addition of the elements of water to the $C_{(2)}=N_{(1)}$ bond of the 5-diazopyrimidine molecule with subsequent opening of the pyrimidine ring and reaction of the resulting amino group with the diazo group, which also leads to the formation of a 1,2,3-triazole ring. A similar mechanism was previously proposed in the case of the formation of acroleyl-1,2,3-triazoles by diazotization of some 3-aminopyridines [9].

In order to ascertain the effect of the character of the substituent in the 2 position of 6-substituted 5-amino-4-chloropyrimidines on the course of the transformation that we observed we studied the behavior of 2-methyl-4,6-dichloro-5-aminopyrimidine (Id) and its 6-methoxy-substituted derivative (Ie) under diazotization conditions. We found that the introduction of a methyl group in the 2 position of these pyrimidine derivatives does not affect the structures of the resulting compounds. Thus treatment of 2-methyl-4,6-dichloro-5-aminopyrimidine with $NaNO_2$ in aqueous HCl led to 4-chloro-5-cyanotriazole (IIa), whereas 2-methyl-4-methoxy-6-chloro-5-aminopyrimidine was converted to 4-carbomethoxy-5-chlorotriazole (IIb) under similar conditions.

EXPERIMENTAL

The IR spectra of mineral oil suspensions, KBr pellets, or solutions in CCl_4 were recorded with a Perkin-Elmer 457 spectrometer. The mass spectra were obtained with an MKh-1303 spectrometer.

2-Methyl-4,6-dichloro-5-aminopyrimidine (Ia). A 55-ml sample of glacial acetic acid was added with vigorous stirring to a solution of 30 g (144 mmole) of 2-methyl-4,6-dichloro-5-nitropyrimidine in 250 ml of methanol containing 30 g of iron filings, and the reaction mixture was stirred at 60°C for 2 h. It was then filtered, and the filtrate was evaporated to dryness. The residue was extracted with ethyl acetate (three 100-ml portions), and the extract was treated with 100 ml of 1 N NaOH solution. The extract was filtered, washed with water until the wash water was neutral, dried with Na_2SO_4, and evaporated to give 23 g (83%) of pyrimidine Ia (a white crystalline substance) with mp 70-71°C (from hexane) (mp 70-72°C [10]).

2-Methyl-4-methoxy-5-amino-6-chloropyrimidine (Ie). A solution of sodium methoxide in methanol (from 0.8 g of Na and 50 ml of methanol) was added to a solution of 3 g (16.8 mmole) of pyrimidine Id in 150 ml of methanol, and the mixture was maintained at room temperature for 12 h. The methanol was then evaporated, and the residue was treated with 50 ml of boiling hexane to give 2.8 g (97%) of white crystalline Ie with mp 56-58°C (from hexane) (mp 60-61°C [10]).

4-Ethoxy-5-amino-6-chloropyrimidine (Ic). This compound was obtained under the conditions used for the synthesis of Ie. Treatment of 3 g of pyrimidine Ia with sodium ethoxide solution, obtained from 0.41 g of Na and 50 ml of ethanol, gave 2.5 g (79%) of a white crystalline substance with mp 52-54°C (from cyclohexane). Found: C 41.2; H 4.5; N 24.6%. $C_6H_8ClN_3O$. Calculated: C 41.5; H 4.6; N 24.2%.

4-Chloro-5-cyano-1,2,3-triazole (IIa). A) A solution of 0.8 g (11.5 mmole) of $NaNO_2$ in 7 ml of water was added dropwise at −5°C to a solution of 1 g (6 mmole) of 4,6-dichloro-5-aminopyrimidine (Ia) in 60 ml of 10% aqueous HCl, and the mixture was maintained at −5°C for 1.5 h and at 20°C for another 1.5 h, after which it was extracted with ether (four 50-ml portions). The ether extract was washed with water until the wash water was neutral, dried with Na_2SO_4, and evaporated to dryness to give 0.7 g (98%) of white crystalline IIa with mp 149-150°C (from benzene–hexane). IR spectrum: 3210 and 2264 cm^{-1} (NH, CO). Found: C 28.0; H 0.8; Cl 27.3; N 43.4%; M^+ 128. C_3HClN_4. Calculated: C 28.0; H 0.8; Cl 27.6; N 43.6%; M 128.

B) This compound was also obtained in 95% yield under the conditions in method A by treatment of 1 g (5.6 mmole) of Id with an aqueous solution of 0.72 g (10.4 mmole) of $NaNO_2$. With respect to its melting point and IR and mass-spectral data, the product was identical to triazole IIa.

4-Carbomethoxy-5-chloro-1,2,3-triazole (IIb). A) This compound was obtained by treatment of 1 g (6.2 mmole) of 4-methoxy-5-amino-6-chloropyrimidine (Ib) with an aqueous solution of 0.8 g (11.5 mmole) of $NaNO_2$ using a procedure similar to that employed for the preparation of IIa (method A). Workup gave white crystalline triazole IIb, with mp 138-139°C (from cyclohexane), in 84% yield. IR spectrum (mineral oil): 2600-2800 broad and 1740 cm^{-1} (associated NH, CO); (KBr): 1735 cm^{-1} (CO); (0.005% solution in CCl_4): 3430 and 1740 cm^{-1} (NH, CO). Found: C 29.6; H 2.4; Cl 21.8; N 26.3%. $C_4H_4ClN_3O_2$. Calculated: C 29.7; H 2.5; Cl 22.0; N 26.0%.

B) This compound was also obtained in 88% yield by treatment of 1.3 g (7.6 mmole) of pyrimidine Ie with an aqueous solution of 1 g (14.5 mmole) of $NaNO_2$ by a method similar to that used to prepare IIa (method A). With respect to its melting point and IR and mass spectra, the product was identical to triazole IIb.

4-Carbethoxy-5-chloro-1,2,3-triazole (IIc). This compound was obtained by treatment of 1 g (4.7 mmole) of pyrimidine Ic with an aqueous solution of 0.77 g (11.1 mmole) of $NaNO_2$ by a procedure similar to that used to prepare triazole IIa (method A). The reaction mixture was maintained at room temperature for 1.5 h, after which 0.5 g of triazole IIc was removed by filtration. The filtrate was extracted with ethyl acetate (three 45-ml portions) to give another 0.3 g of IIc for an overall yield of 80%. The white crystalline product had mp 78-79.5°C (from hexane) (mp 78-81°C [7] and 74-77°C [8]). IR spectrum (mineral oil): 3550, 3240, 3150, 1720 (NH, CO); 1500 cm^{-1}. IR spectrum [7] (crystals): 3200, 3150, 1720 (NH, CO); 1500 cm^{-1}; (KBr): 1720 cm^{-1} (CO). IR spectrum [8] (KBr): 1690 cm^{-1}; (0.005% solution in CCl_4): 3435, 1736 cm^{-1} (NH, CO).

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