SOME NUCLEOPHILIC SUBSTITUTION REACTIONS OF s-TRIAZOLO[1,5-c]PYRIMIDINES

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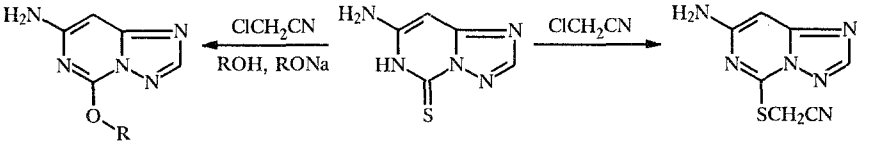
Nucleophilic substitution of 5-methylthio- and 5-cyanomethylthio-7-amino-s-triazolo[1,5-c]pyrimidines has been carried out using sodium hydroxide, ammonia, hydrazine hydrate, and four amines. The cyanomethyl group is particularly reactive under these conditions and 5-cyanomethylthiotriazolopyrimidine can be used to functionalize this heterocycle.

Derivatives of s-triazolo[1,5-c]pyrimidine are interesting physiologically active substances and include known bronchodilators [1], sedatives and hypotensives [2], anti-inflammatories [2, 3], and tranquilizers [4]. In this connection, development of a convenient synthetic method for novel s-triazolo[1,5-c]pyrimidines is an important goal.

We have compared the reactivity of 5-methylthio- and 5-cyanomethylthio-7-amino-s-triazolo[1,5-c]pyrimidines (Ia, b) toward nucleophilic substitution. On this basis we propose methods for preparing the 5-substituted triazolopyrimidines III-VI. The nucleophilic agents used were sodium hydroxide, ammonia, hydrazine hydrate, and four amines.

We have previously described the synthesis of Ia [5]. The cyanomethylthiotriazolopyrimidine Ib has been prepared by treating 7-amino-s-triazolo[1,5-c]pyrimidine-5-thione (II) [5] with chloroacetonitrile in sodium ethylate solution. The reaction does not occur at room temperature but at 60°C a mixture of IIIa and Ib is formed. If the reaction mixture is refluxed, the only product is IIIa which shows the absence of the characteristic cyano group band in the infrared. The PMR spectrum shows proton signals for the pyrimidine (5.98) and triazole (8.0) rings, the amino group (6.45), a triplet (1.4), and quartet (4.4 ppm) which confirm the structure. Analogous use of sodium methylate gives the 5-methoxy derivative IIIb with a proton NMR signal for the CH_3 group at 4.13 ppm. Compound Ib can be obtained in high yield by mixing thione II and chloroacetonitrile at room temperature in the presence of NaOH (10 mmole to 3 mmole II). The IR spectrum of the reaction product shows a cyano group absorption at 2240 cm^{-1} and the PMR spectrum shows signals for the protons of the methylene group at 4.42, the pyrimidine (6.25) and triazole (8.25) rings, and the amino group at 6.85 ppm.



IIIa,b II Ib

IIIa R=Et; b R=Me

We have previously shown [5] that heating Ia with hydrazine hydrate in ethanol leads to nucleophilic substitution of the methylthio group and formation of the 5-hydrazino product. In this work we studied the reaction of Ia with other nucleophilic agents. Refluxing it in NaOH (2 N) gave 7-amino-s-triazolo[1,5-c]pyrimidin-5-one (V), previously reported by us in [6]. Reaction of Ia with ammonia, methyl-, dimethyl-, or benzylamine, and with piperidine occurs under severe conditions by heating in a sealed ampul at 140-150°C. Reaction with ammonia gives the 5,7-diamino derivative VIa in 60% yield. The structure of the latter is confirmed by IR and PMR spectroscopy. The IR spectrum shows amino absorption bands at 3210-3380 cm^{-1}. The PMR spectrum shows signals for protons in the pyrimidine (5.72) and triazole (8.0) rings, and two amino groups at 6.09 and 7.40 ppm. Under these conditions the amino derivatives VIb-e are formed in low yields (25-36%), together with the triazolopyrimidine V and products of unknown structure.

In the case of the 5-cyanomethylthiotriazolopyrimidine Ib the cyanomethyl group is substituted by oxygen even upon short heating in aqueous base (to V) and by amino- or hydrazino-groups at room temperature (to VIa and IV, respectively). Reaction of Ib with methyl-, dimethyl-, and benzylamine or with piperidine also takes place with formation of VIb-e. In all cases the product yields are greater than 70%.

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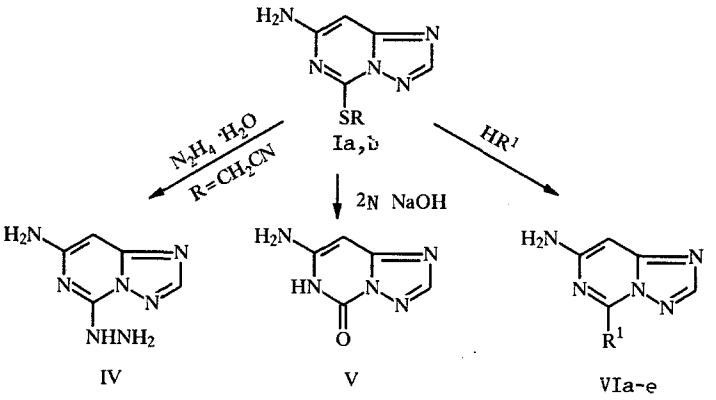

Ia, R = Me; b, R = CH_2CN; VIa, R^1 = NH_2; b, R^1 = NHMe; c, R^1 = $N(Me)_2$; d, R^1 = NHBz; e) R^1-piperidino

These results show that the cyanomethyl group shows high reactivity toward nucleophilic substitution and that the cyanomethylthio derivative Ib can be used for functionalizing the heterocycle.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for KBr tablets. PMR spectra were taken on a Perkin—Elmer R-12B (60 MHz) instrument using DMSO-d_6 solvent and TMS internal standard.

The reactions were monitored using TLC on Silufol UV-254 plates.

Elemental analytical data for C, H, and N agreed with those calculated.

5-Cyanomethylthio-7-amino-s-triazolo[1,5-c]pyrimidine (Ib, $C_7H_6N_6S$). NaOH (2N, 5 ml, 10 mmole) was added to a suspension of II (0.5 g, 2.9 mmole) in chloroacetonitrile (20 ml). The mixture was stirred for 1 h at 20°C and the precipitate filtered and recrystallized from ethanol to give Ib (0.43 g, 69%) with mp 236°C.

5-Ethoxy-7-amino-s-triazolo[1,5-c]pyrimidine (IIIa, $C_7H_9N_5O$). A suspension of II (0.3 g, 1.8 mmole) in anhydrous ethanol (15 ml) was heated to reflux and chloroacetonitrile (0.14 g, 2.51 mmole) added. The mixture was refluxed for 2 h with stirring, filtered, the filtrate evaporated to dryness at reduced pressure, and the residue recrystallized from ethanol. Yield 0.25 g (78%) with mp 206°C.

5-Methoxy-7-amino-s-triazolo[1,5-c]pyrimidine (IIIb, $C_6H_7N_5O$) was obtained similarly to IIIa from II (0.3 g, 1.8 mmole), sodium methylate (0.12 g, 2.2 mmole), and chloroacetonitrile (0.2 ml, 2.51 mmole) giving 0.25 g (86%) with mp 252°C.

5-Hydrazino-7-amino-s-triazolo[1,5-c]pyrimidine (IV, $C_5H_7N_7$). Hydrazine hydrate (1 ml, 20.5 mmole) was added to Ib (0.3 g, 1.65 mmole) in ethanol (10 ml). The mixture was stirred for 15 min, the precipitate filtered and recrystallized from water with charcoal. Yield 0.21 g (88%) with mp 290°C.

7-Amino-s-triazolo[1,5-c]pyrimidin-5-one (V, $C_5H_5N_5O$). A. A solution of Ia (0.5 g, 2.9 mmole) in NaOH (2N, 25 ml) was refluxed for 5 h, cooled, and filtered. The filtrate was neutralized with acetic acid to pH 5. The precipitate was filtered and twice recrystallized from water to give 0.33 g (79.1%) with mp 300°C.

B. A solution of Ib (0.5 g, 2.6 mmole) in NaOH (2N) was refluxed for 10 min and worked up as in method **A** to give 0.37 g (88%) with mp 300°C.

5,7-Diamino-s-triazolo[1,5-c]pyrimidine (VIa, $C_5H_5N_6$). A. A suspension of Ia (1.0 g, 5.5 mmole) in aqueous ammonia (25%, 30 ml) was heated at 140-150°C for 5 h. The precipitate was filtered and recrystallized from water to give 0.50 g (60%) with mp 245°C.

B. A suspension of Ib (0.5 g, 2.6 mmole) in aqueous ammonia (25%, 15 ml) was stirred at 20°C for 30 min. The precipitate was filtered and recrystallized from water to give 0.33 g (90%) with mp 245°C.

5-Methylamino-7-amino-s-triazolo[1,5-c]pyrimidine (VIb, $C_6H_8N_6$) was obtained similarly to VIa from Ia (0.3 g, 1.65 mmole) and aqueous methylamine (25%, 10 ml) (method **A**) or from Ib (0.5 g, 2.6 mmole) in aqueous methylamine (25%, 10 ml) (method **B**). The reaction product (method **A**) was evaporated to dryness at reduced pressure, the residue triturated with acetone and ethanol, and recrystallized from aqueous ethanol to give 0.16 g (55.5%) with mp 207°C.

The precipitate (method **B**) was filtered and recrystallized from aqueous ethanol to give 0.31 g (78%) with mp 207°C.

5-Dimethylamino-7-amino-s-triazolo[1,5-c]pyrimidine (VIc, $C_7H_{10}N_6$) was obtained similarly to VIb from Ia (0.3 g, 1.65 mmole) (method **A**) or from Ib (0.5 g, 2.6 mmole) (method **B**) and aqueous dimethylamine solution (33%, 10 ml) to give 0.2 g (68%) (method **A**) or 0.24 g (61%) (method **B**) with mp 278°C.

5-Benzylamino-7-amino-s-triazolo[1,5-c]pyrimidine (VId, $C_{12}H_{12}N_6$) was obtained similarly to VIb from Ia (0.3 g, 1.65 mmole) (method **A**) or Ib (0.5 g, 2.6 mmole) (method **B**) and benzylamine (10 ml). The reaction product was diluted with a threefold excess of water and the precipitate filtered, washed with ethanol, and recrystallized from aqueous ethanol to give 0.14 g (35.9%) (method **A**) or 0.34 g (72%) (method **B**) with mp 210°C.

5-Piperidino-7-amino-s-triazolo[1,5-c]pyrimidine (VIe, $C_{10}H_{14}N_6$) was prepared similarly to VIa from Ia (0.3 g, 1.65 mmole) (method **A**) or Ib (0.5 g, 2.6 mmole) (method **B**) and piperidine (1 ml, 10 mmole) in water (10 ml) to give 0.21 g (25.3%) (method **A**) or 0.48 g (90%) (method **B**) with mp 183°C.

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