Pyrimidine Derivatives and Related Compounds. XXVII. Reaction of 6-Cyano-1,3-dimethyluracil with Nucleophiles

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Reaction of 6-cyano-1,3-dimethyluracil (1) with some nucleophilic reagents such as sodium hydroxide, sodium methoxide, alcohols, butylamine, and hydrazines gave 5-cyano- (2; cine-substitution product), 6-methoxy- (3), 6-butyramino- (10a), 6-hydrazino-1,3-dimethyluracil (10b) and imidates of 1. Reaction of 5-bromo-6-cyano-1,3-dimethyluracil (5) with hydrazine hydrate gave 6-amino-1,3-dimethyluracil (11), which was also obtained by reaction of 5-bromo-6-chloro-1,3-dimethyluracil (12) with hydrazine hydrate.

In the previous paper, we reported the synthesis of 6-cyanouracil derivatives which are of interest in their reactivities due to the presence of a cyano group at β-position to the enamidoketone of a uracil nucleus. During the investigation, we found that 6-cyano-1,3-dimethyluracil (1) was readily converted to 5-cyano-1,3-dimethyluracil (2) when heated with a catalytic amount of sodium cyanide in dimethylformamide (DMF). This conversion is a cine-substitution of the β-cyano group of the enamidoketone system with a nucleophilic reagent. Succeeding to the above study, we describe here the reaction of 1 with some nucleophiles such as sodium hydroxide, sodium methoxide, alcohols, amines, and hydrazines. Such a reaction caused a conversion to 5-position, substitution at 6-position, or addition to the cyano group depending on a property of the nucleophilic reagent used and reaction conditions applied.

Reaction with OH-

In order to extend the conversion of 1 to 2 with a cyanogen ion, the use of some sulfur-containing nucleophilic reagents, such as NaSH, Na₂SO₃, NaHSO₃ etc. which are known to attack across the 6,6-double bond of 5-bromouracils, was attempted, but no conversion took place and only the starting material was recovered. When 1 was, however, heated in the presence of a catalytic amount of sodium hydroxide in DMF, the conversion occurred giving the aimed 2. It seems reasonable to assume the mode of the reaction to be as follows.

![Chart 1](image)

2) a) A part of this work was reported in a communication: S. Senda, K. Hirota, and T. Asao, Tetrahedron Letters., 1973, 2647; b) This work was presented at the 7th Congress of Heterocyclic Chemistry, Chiba, 1974 (Abstracts of Papers, p. 140.)
3) Location: 492-36, Mitakata, Gifu.
Thus, a key step of the reaction is not a direct nucleophilic C-5 attack of OH\textsuperscript{-} to 1 but hydrolysis of a part of 1 with an alkali leading to formation of 1,3-dimethylbarbituric acid together with sodium cyanide. A catalytic amount of the resulting cyanogen ion might give rise to the C-5 attack to 1 and, as a result, the usual conversion subsequently occurred to give 2.

The reaction of 1 with other nucleophilic reagents, e.g. sodium methoxide, alcohols, amines, and hydrazines, however, caused different type of reactions which proves that the conversion of the above type is characteristic of a cyanogen ion.

**Reaction with Alcohols**

Treatment of 1 with an equimolar sodium methoxide in refluxing methanol afforded 1,3-dimethyl-6-methoxyuracil (3) in 75\% yield. Such a facile substitution should not be unexpected, because 4-cyano-2,6-dimethylpyrimidine is already known to react with sodium methoxide giving 4-methoxy-2,6-dimethylpyrimidine.\(^8,9\) On the other hand, when 1 was refluxed in the presence of a catalytic amount of sodium methoxide, the isolated product was neither 2 nor 3 but a methyl imidate (4a). Compound 4a was also obtained by using a catalytic amount of potassium hydroxide as an alkali, instead of sodium methoxide. The structure of 4a was confirmed by its spectral and elemental analyses. The elemental analysis was in agreement with C\textsubscript{8}H\textsubscript{10}O\textsubscript{3}N\textsubscript{3} which corresponds to an addition of 1 mole of methanol to 1. There was no absorption in the 2260—2210 cm\textsuperscript{-1} region in the infrared (IR) spectrum, thus showing the absence of the cyano group, while there was a strong NH band at 3330 cm\textsuperscript{-1}. The proton magnetic resonance (PMR) spectrum of 4a indicated a sharp singlet at \(\delta 3.92\), characteristic of a methoxy group.

It was of interest to note that the reaction of 1 with sodium methoxide gave 3 or 4 depending on the amount of the alcoholate used. Such a difference would be due to its structural peculiarity that the electron withdrawing 6-cyano group was substituted at the \(\beta\)-position to the enamidoketone system of a uracil nucleus \(\left(\text{C}=\text{C} \equiv \text{C} \equiv \text{N}^\equiv\right)\). Namely, the strong nucleophiles such as CH\textsubscript{3}O\textsuperscript{-} attack on the electron poor C-6 position, while the weak nucleophiles

![Chemical structures](chart)

such as MeOH attack on the CaN triple bond. In the latter case the resulting imidate might to be stabilized by the electron-deficient uracil ring.  

The usual method for synthesizing imidates from nitriles is an introduction of hydrogen chloride gas into an alcohol-nitrile mixture, known as the Pinner Reaction. On the other hand, it has been recently found that some heteroaromatic nitriles readily form the corresponding imidates in alkaline media. For example, Schaefer, et al., and Yamada, et al., independently isolated the imidate from 2-cyanopyridine in good yields. In this connection, we have decided to carry out a further investigation on the formation of an imidate in several alcohols as well as reactions of the resulting imidate.

Compound 1 reacted with lower alcohols such as methanol and ethanol in the presence of a catalytic amount of potassium hydroxide to give the corresponding imidates 4a, b in good yields. However, the reaction with primary alcohols of 3 and 4 carbon atoms such as propyl alcohol, butyl alcohol, and isobutyl alcohol gave a mixture of the corresponding imidate and 6-alkoxyuracil, which was detected by the PMR spectra. The proportion of the imidate decreased according to the lengthening of the chain of alcohols. When 1 was treated with isopropyl alcohol, sec-butyl alcohol, or tert-butyl alcohol, the isolation of an imidate was also unsuccessful. In this case, the starting material was recovered quantitatively. This might be due to the steric hindrance of secondary or tertiary alcohols on their addition to the cyano group. While C-5 substituents had no influence on the formation of imidate because 5-bromo-6-cyano-1,3-dimethyluracil (5) obtained by bromination of 1 gave the methyl imidate (6) in alkaline media in good yield.

We have reported that base-catalyzed hydrolysis of 4a with 5% aqueous solution of sodium hydroxide gives 6-carbamoyl-1,3-dimethyluracil (8), while acid-catalyzed hydrolysis of 4a using 10% hydrochloric acid gave 1,3-dimethyluracil methyl ester (7). Although imidates are generally converted to amidine salts by treating with a variety of ammonium salts, 4a failed to give such an amidine salt and afforded 8 when heated with ammonium chloride, methylamine, hydrochloride, or aniline hydrochloride. The reaction might involve an unstable imidate hydrochloride (9) as an intermediate although 9 could not be actually isolated by passing dry hydrogen chloride gas into the benzene solution of 4a at room temperature. Anyhow, 9 might then be dechloromethylated to afford 8. Treatment of 4a with a chlorinating agent, e.g., SOCl₂, POCl₃, and PCl₃ at room temperature also yielded 8. Refluxing of 4a in phosphorus oxychloride gave 1. It is probably due to the dehydration of 8.

Reaction with Amines and Hydrazines

Heating of 1 with butylamine and hydrazine hydrate in the absence of a solvent gave 6-butylamino-(10a) and 6-hydrazino-1,3-dimethyluracil (10b) in 76% and 59% yields, respectively. 5-Bromo-6-cyano-1,3-dimethyluracil (5) underwent vigorous exothermic reaction in hydrazine hydrate at room temperature with evolution of ammonia and nitrogen, affording an abnormal product, 6-amino-1,3-dimethyluracil (11) in 66% yield, which was also prepared in 64% yield from 5-bromo-6-chloro-1,3-dimethyluracil (12) and hydrazine hydrate under the same conditions as above.

In order to investigate the reaction mechanism, the Hofmann reaction of 8 and 5-bromo-6-carbamoyl-1,3-dimethyluracil (13) was carried out because they are expected to be as poten-

10) Negative substituents on the nitrile have a stabilizing effect on the corresponding imidates: H.C. Brown and C.R. Wetzel, *J. Org. Chem.*, 30, 3724 (1965), and the references cited therein.
tial intermediates, but the reaction failed to give 11 and both the starting materials were recovered quantitatively. From the above results, we tentatively suggest the mechanism outlined in Chart 4. The first step would be simple substitutions of both 5-bromine and 6-cyano (or 6-chlorine) in 5 or 12 by hydrazine affording 5,6-dihydrazino compound 14. The second step might be an intramolecular nucleophilic addition. The resulting cyclic intermediate (15) may undergo an elimination of ammonia, followed by a cleavage of the triazole ring (16) and a release of nitrogen, leading to the final product (11). Attempt to isolate such intermediates (14), (15) and (16) were, however, unsuccessful.

Treatment of 5 with hydrazines such as hydrazine hydrate and methylhydrazine in aqueous solution under reflux yielded 13. During the course of the hydrolysis, a hydrazine-adduct (17) is supposed to be formed as an intermediate. It is similar to the reaction of 1 to 8 via the imidate (4).

Experimental

5-Cyano-1,3-dimethyluracil (2)——To a solution of 500 mg (3 mmole) of 1 in 5 ml of DMF were added 12 mg (0.3 mmole) of sodium hydroxide and two drops of water. The mixture was heated at 80—90° for

15) Melting points were taken on a Yanagimoto Micro Melting Point apparatus and are uncorrected. IR spectra were recorded on Hitachi 215 spectrophotometer as KBr pellets. PMR spectra were measured on a Hitachi Perkin-Elmer R-20B spectrometer using tetramethylsilane as internal standard.
2 hr and the solution was evaporated in vacuo. The residue was washed with water to give 400 mg (80%) of the crude product, mp 152°-158°. Recrystallization from ethanol yielded colorless needles of 2, mp 164°-165°, which was identified with an authentic sample by IR spectrum and mixture melting point test.

1,3-Dimethyl-6-methoxyuracil (3)—A mixture of 830 mg (5 mmole) of 1 and 540 mg (10 mmole) of sodium methoxide, prepared from 230 mg of sodium in 20 ml of absolute methanol, was refluxed for 1.5 hr. After cooling, the precipitate was collected by filtration, dissolved in 5 ml of water. After acidification with hydrochloric acid, the solution was extracted with chloroform. The extract was dried and evaporated in vacuo to give 630 mg (75%) of white crystals of the crude product, mp 150°-156°. Recrystallization from methanol afforded white needles of 3, mp 165°-166° (lit. mp 164°-165°). PMR (CDCl₃) δ: 3.33 (3H, s, NCH₃), 3.36 (3H, s, NCH₃), 3.88 (2H, s, OCH₃), 5.13 (1H, s, 5-CH). Anal. Calcd. for C₃H₅N₂O₂: C, 49.40; H, 5.92; N, 16.46. Found: C, 48.37; H, 5.85; N, 16.33.

Methyl 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-carboximidate (4a)—A mixture of 830 mg (5 mmole) of 1 and 23 mg of sodium methoxide, prepared from 10 ml of methanol (0.43 mmole) of sodium in 20 ml of absolute methanol, was refluxed for 1 hr. The solution was concentrated to ca. 5 ml and cooled. The resulting colorless crystals were collected by filtration. Recrystallization from ligroin gave 650 mg (66%) of 4a, mp 120°. IR: 3430 cm⁻¹ (NH). PMR (CDCl₃) δ: 3.36 (6H, s, 2NCH₃), 3.92 (3H, s, OCH₃), 5.82 (1H, s, 5-CH), 7.90 (1H, bs, NH). Anal. Calcd. for C₃H₇N₂O₂: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.89; H, 5.60; N, 21.41.

b) To a suspension of 830 mg (5 mmole) of 1 in 10 ml of methanol was added 28 mg (0.5 mmole) of potassium hydroxide. The mixture was refluxed for 1 hr. After neutralization with hydrochloric acid, the solution was evaporated in vacuo and the residue was triturated with 1 ml of cold water. Filtration then gave colorless crystals of 4a in 80% yield, identical with a sample prepared in method a.

Ethyl 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-carboximidate (4b)—A mixture of 830 mg (5 mmole) of 1 and 28 mg (0.5 mmole) of potassium hydroxide in 10 ml of ethanol was treated by the same procedure as described for the preparation of 4a in method b) to give 900 mg (85%) of 4b, mp 98°-100°. IR: 3430 cm⁻¹ (NH). PMR (CDCl₃) δ: 1.39 (3H, t, J=8 Hz, CH₂CH₃), 3.38 (6H, s, 2NCH₃), 4.35 (2H, q, J=8 Hz, OCH₂), 5.81 (1H, s, 5-CH). Anal. Calcd. for C₃H₇N₂O₂: C, 51.17; H, 6.20; N, 19.90. Found: C, 50.89; H, 6.06; N, 20.06.

5-Bromo-6-cyano-1,3-dimethyluracil (5)—To a solution of 830 mg (5 mmole) of 1 in 10 ml of chloroform was obtained 400 mg of bromine. After standing for 30 min, the reaction solution was evaporated in vacuo. The residue was recrystallized from methanol to give 510 mg (83%) of 5, mp 123°-125°. PMR (CDCl₃) δ: 3.46 (3H, s, NCH₃), 3.70 (3H, s, NCH₃). Anal. Calcd. for C₃H₅N₂O₄Br: C, 34.45; H, 2.48; N, 17.22. Found: C, 34.55; H, 2.55; N, 17.17.

Methyl 5-Bromo-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-carboximidate (6)—A mixture of 600 mg (2.5 mmole) of 5 and 14 mg (0.25 mmole) of potassium hydroxide in 5 ml of methanol was treated by the same procedure for the preparation of 4a in method b) to give 570 mg (82%) of the crude product, mp 135°-137°. Recrystallization from water gave white needles of 6, mp 137°. IR: 3430 cm⁻¹ (NH). PMR (CDCl₃) δ: 3.40 (3H, s, NCH₃), 3.44 (3H, s, NCH₃), 3.99 (3H, s, OCH₃), 7.50 (1H, very bs, NH). Anal. Calcd. for C₃H₇N₂O₄Br: C, 34.81; H, 3.65; N, 15.23. Found: C, 34.82; H, 3.64; N, 15.09.

1,3-Dimethylorotic Acid Methyl Ester (7)—A suspension of 490 mg (2.5 mmole) of methyl imidate (4a) in 10 ml of 10% hydrochloric acid was refluxed for 15 min, while the product then crystallized directly from the hot reaction solution. After cooling, the white solid was collected by filtration to give 300 mg (61%) of 7, mp 65°-68°. The analytical sample, recrystallized from methanol, melted at 70°-74° (lit. mp 76°-77°). Anal. Calcd. for C₂H₇O₂N₂: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.68; H, 5.20; N, 14.05.

6-Carbamoyl-1,3-dimethyluracil (8)—A mixture of 400 mg (2.5 mmole) of 4a and 161 mg (3 mmole) of ammonium chloride in 10 ml of DMF was heated under reflux for 1 hr. The solution was evaporated in vacuo. Trituration of the residue with 10 ml of cold water followed by filtration gave 300 mg (65%) of the crude product of 8. Recrystallization from methanol gave colorless needles of 8, mp 268°-240°, identical with an authentic sample.⁹

³ Compound 4a was treated with 3 equivalents of methyamine hydrochloride instead of ammonium chloride by the same procedure as described above to give 8 in 60% yield.

b) A mixture of 490 mg (2.5 mmole) of 4a and 390 mg (3 mmole) of aniline hydrochloride was placed in a test tube, which was immersed in an oil bath preheated to 150°. The temperature of the heating bath was then raised to 200° over a period of 20 min. The contents of the reaction vessel were cooled, triturated with ether, and filtrated. Recrystallization from methanol gave 350 mg (76%) of 8, identical with a sample prepared in method a).

c) To 0.5 ml of thionyl chloride was added 490 mg (3 mmole) of 4a. The mixture was stirred at room temperature for 1 hr. The white solid which was crystallized directly from the reaction solution was collected.

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by filtration to give 250 mg (55%) of 8, identical with a sample prepared in method a).

Compound 4a (490 mg) was treated in 1 ml of phosphorus oxychloride by the same procedure as described above to give 8 in 52% yield.

d) A mixture of 490 mg (2.5 mmole) of 4a and 620 mg (3 mmole) of phosphorus pentachloride was placed in a test tube, which was immersed in an oil bath preheated to 100°. The temperature of the heating bath was raised to 150° over a period of 30 min. The contents of the reaction vessel were cooled, triturated with water, and filtered. Recrystallization from methanol gave 275 mg (60%) of 8, identical with a sample prepared in method a).

6-Cyano-1,3-dimethyluracil (1) — A suspension of 490 mg (2.5 mmole) of methyl imidate (4a) in 5 ml of phosphorus oxychloride was refluxed for 30 min. The solution was evaporated in vacuo. Trituration of the residue with 5 ml of cold water followed by filtration gave 380 mg (83%) of white solid of 1. Recrystallization from ethanol gave material identical with an authentic sample.4

6-Butylamino-1,3-dimethyluracil (10a) — To a 10 ml of butylamine was added 830 mg (5 mmole) of 1. The mixture was refluxed for 3 hr. The reaction solution was evaporated in vacuo. The residue was triturated with ether, collected by filtration, and washed with ether to give 0.8 g (76%) of the crude product of 10a, mp 135—138°. The analytical sample, recrystallized from benzene, melted at 141—142° (lit.18) mp 143°. Anal. Calcd. for C₉H₁₁N₂O₂: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.62; H, 8.09; N, 19.89.

6-Hydrazino-1,3-dimethyluracil (10b) — A mixture of 830 mg (5 mmole) of 6-cyano-1,3-dimethyluracil and 600 mg (12 mmole) of hydrazine hydrate was heated at 100° for 30 min. The contents of the reaction vessel were triturated with 10 ml of ethanol. The precipitate was collected by filtration and washed with ethanol to give 590 mg (51%) of 10b, mp 226—229° (decomp.), which was identified with an authentic sample prepared by the procedure of Pfeiderer.19

6-Amino-1,3-dimethyluracil (11) — a) To 610 mg (2.5 mmole) of 5 was gradually added 500 mg of hydrazine hydrate at room temperature, while the reaction proceeded with violence. After standing for 1 hr at room temperature, the reaction mixture was added to 10 ml of water, and the precipitate was collected by filtration and washed with water to give 260 mg (66%) of 11, mp >300° (from ethanol), identical with an authentic sample (lit.19) mp >300°. IR: r₅ max 3240, 3420 cm⁻¹ (NH₂). PMR (DMSO-d₆) δ: 3.10 (3H, s, NCH₃), 3.28 (3H, s, NCH₃), 4.72 (1H, s, 5-CH), 6.78 (2H, bs, NH₂). Anal. Calcd. for C₅H₉O₂N₂: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.55; H, 5.84; N, 27.92.

b) Compound 12 (610 mg, 2.5 mmole) was treated with 500 mg of hydrazine hydrate as described above to give 250 mg (64%) of 11.

5-Bromo-6-carbamoyl-1,3-dimethyluracil (13) — a) A suspension of 610 mg (2.5 mmole) of 5 and 250 mg (5 mmole) of hydrazine hydrate in 6 ml of water was refluxed for 20 min. After cooling, the white crystals were collected by filtration and washed with water to give 320 mg (49%) of the crude product, mp 290—294°. Recrystallization from water gave colorless needles of 13, mp 299°. Anal. Calcd. for C₅H₄BrN₂O₂: C, 32.09; H, 3.08; N, 16.04. Found: C, 32.31; H, 3.10; N, 16.06.

b) A mixture of 610 mg (2.5 mmole) of 5 and 160 mg of methylhydrazine in 6 ml of water was treated as described above to give 390 mg (80%) of 13, identical with a sample prepared in method a).