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PYRROLOPYRIMIDINES. 4.* A CONVENIENT METHOD FOR THE PRODUCTION OF 6-(2-AMINOVINYL)-5-NITROPYRIMIDINES AND THEIR TRANSFORMATION INTO PYRROLO[3,2-*d*]PYRIMIDINES

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A convenient method is proposed for the production of 6-(2-aminovinyl)pyrimidine-2,4-diones, involving the reaction of 6-methyluracils with triethyl orthoformiate and secondary amines.

Keywords: secondary amines, pyrrolo[3,2-*d*]pyrimidines, triethyl orthoformiate, uracils.

It is well known that one of the best methods for the production of pyrrolo[3,2-*d*]pyrimidines is the reductive cyclization of 5-nitro-6-(2-dimethylaminovinyl)pyrimidines, e.g., the transformation of the substituted pyrimidine **2a** into the product **3** [2, 3] (see the scheme). Compounds of type **2a** are usually synthesized by treating the corresponding 6-methylnitrouracils with dimethylformamide dimethyl acetal [2, 3]. However, the preparation of the latter is an extremely laborious process, and it is therefore more expedient to find a sufficiently convenient replacement for this reagent. It was known from the published data that 2-methylpyrylium salts react with ethyl orthoformiate in acetic acid in the presence of primary aromatic amines, forming 2-arylaminovinylpyrylium salts [4]. In the present work we tried to use the method for the production of the substituted 6-(aminovinyl)pyrimidine-2,4-diones **2**.

We found that 5-nitro-1,3,6-trimethyluracil (**1**) forms the corresponding 6-aminovinyl derivatives **2b-f** with yields of 37-81% when it is heated with an excess of triethyl orthoformiate in the presence of various secondary amines, such as piperidine, morpholine, diphenylamine, N-methylaniline, and N-benzylaniline. Attention is drawn to the fact that both highly basic (piperidine, morpholine, piperazine) and weakly basic aryl- and diarylamines enter into the reaction equally well. With piperazine the only isolated reaction product was the derivative of 1,4-divinylpyrazine **2g** (yield 71%).

In the case of morpholine it was shown that 6-methyl-5-nitrouracil and also 1,3,6-trimethyluracil enter into an analogous reaction, resulting in the formation of compounds **2h** and **2i** respectively. The formation of the latter product indicates that the presence of nitro at position 5 of the 6-methyluracil ring is not an essential condition for the transformation to the 6-aminovinyl derivative. The CP acidity of the CH_3 group required for the reaction is probably secured fully by resonance stabilization of the intermediately formed carbanion.

* For Communication 3, see [1].

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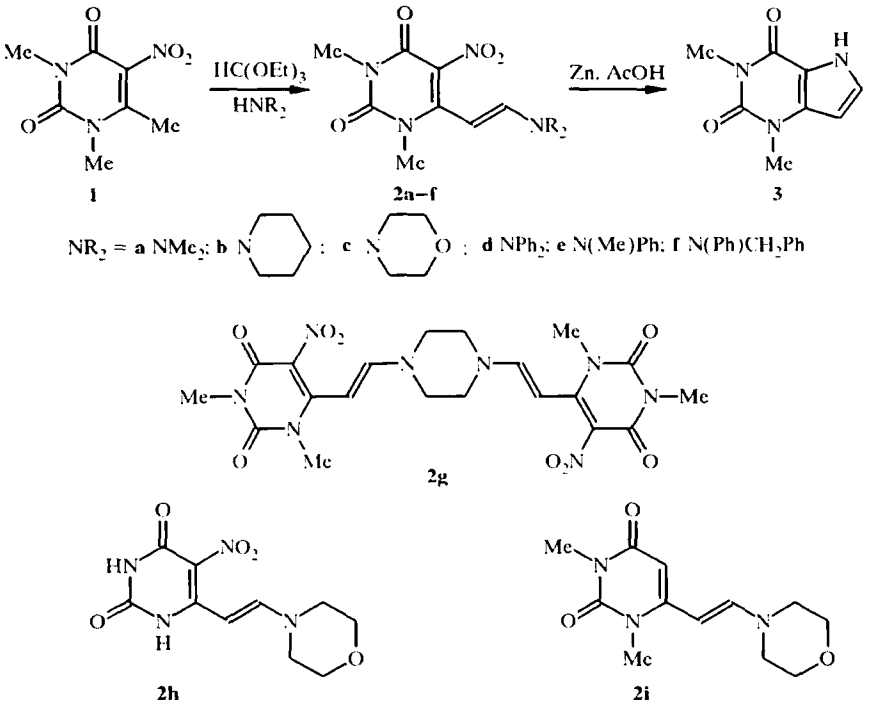

The replacement of triethyl orthoformiate by triethyl orthoacetate did not lead to satisfactory results. In spite of outward signs of reaction (a deep red color) only the initial compound was isolated from the reaction mixture.

We established that the enamines **2b,c**, like **2a**, readily undergo reductive cyclization when boiled with zinc in acetic acid, resulting in the formation of compound **3** in good yields (67-71%). Nevertheless, the principal aim of the work, i.e., improvement of the method for the production of pyrrolo[2,3-*d*]pyrimidine-2,4-diones from 5-nitro-6-methyluracils, was achieved.

EXPERIMENTAL

The IR spectra were obtained in vaseline oil on an IKS-40 spectrometer. The ^{1}H NMR spectra were obtained on a Varian Unity 300 spectrometer with TMS as internal standard. The reactions and the individuality of the compounds were monitored on Silufol UV-254 plates and on aluminum oxide of II activity with chloroform as eluant and iodine vapor as developer. The melting points were determined in sealed glass capillaries and were not corrected.

1,3-Dimethyl-5-nitro-6-(2-piperidinovinyl)pyrimidine-2,4(1H,3H)-dione (2b). A mixture of compound **1** (20 g, 0.1 mol), triethyl orthoformiate (100 ml), and piperidine (26.4 g, 0.31 mol) was boiled for 3 h and then evaporated to approximately half volume. After cooling, ethanol (100 ml) and water (250 ml) were added to the crystallizing mass. The orange-red crystals of the product **2b** were filtered off, washed successively with water and with ethanol, and dried in air. Yield 21.4 g (73%); mp 172-173°C (dioxane). IR spectrum, cm^{-1}: 1690, 1632 (CO). ^{1}H NMR spectrum ($CDCl_3$), ppm: 6.85 (1H, d, J_{trans} = 12.98 Hz, CH=CH–N); 4.65 (1H, d, J = 12.98 Hz, CH=CH–N); 3.44 (3H, s, 1-CH_3); 3.34 (3H, s, 3-CH_3); 3.28-3.25 (4H, m, 2'- and 6'-CH_2); 1.66-1.61 (6H, m, 3'-, 4'-, and 5'-CH_2). Found, %: C 53.12; H 6.10; N 19.17. $C_{13}H_{18}N_4O_4$. Calculated, %: C 53.05; H 6.16; N 19.04.

1,3-Dimethyl-6-(2-morpholinovinyl)-5-nitropyrimidine-2,4(1H,3H)-dione (2c). A solution of compound **1** (43.6 g, 0.22 mol) and morpholine (59.2 g, 0.68 mol) in triethyl orthoformiate (100 ml) was boiled for 4.5 h. Ethanol (100 ml) and water (40 ml) were added to the cooled crystallizing mass. After 1 h the orange-red crystals were filtered off and washed with water and with alcohol. The yield was 52.5 g (81%); mp 170-172°C

(dioxane). IR spectrum, cm^{-1}: 1705, 1640 (CO). ^1H NMR spectrum ($CDCl_3$), ppm: 6.79 (1H, d, J_{trans} = 13.18 Hz, CH=CH–N); 4.70 (1H, d, J = 13.18 Hz, CH=CH–N); 3.71 (4H, t, 2'- and 6'-CH_2); 3.42 (3H, s, 1-CH_3); 3.31 (3H, s, 3-CH_3); 3.25 (4H, t, 3'- and 5'-CH_2). Found, %: C 48.56; H 5.23; N 19.17. $C_{12}H_{16}N_4O_5$. Calculated, %: C 48.65; H 5.44; N 18.91.

1,3-Dimethyl-6-(2'-diphenylaminovinyl)-5-nitropyrimidine-2,4(1H,3H)-dione (2d). A mixture of compound **1** (1 g, 5 mmol); diphenylamine (2.62 g, 15 mmol), and triethyl orthoformiate (15 ml) was boiled for 6 h, after which it was evaporated to dryness under vacuum. The residue was treated with ether (70-100 ml). The crude substance was filtered off and washed with 5-10 ml of ether. To remove the unreacted diphenylamine the product was purified on a column of silica gel with a 1:1 mixture of ethyl acetate and chloroform as eluant. The yellow fraction (R_f 0.7) was collected. After evaporation we obtained 0.81 g (43%) of the product **2d** in the form of bright yellow crystals; mp 188-189°C (benzene). IR spectrum, cm^{-1}: 1713, 1657 (CO). ^1H NMR spectrum ($CDCl_3$), ppm: 7.49 (1H, d, J_{trans} = 13.40 Hz, CH=CH–N); 7.39 (4H, m, C_6H_5, *m*-H); 7.27 (2H, m, C_6H_5, *p*-H); 7.06 (4H, m, C_6H_5, *o*-H); 4.87 (1H, d, J = 13.40 Hz, CH=CH–N); 3.36 (3H, s, 1-CH_3); 3.28 (3H, s, 3-CH_3). Found, %: C 63.84; H 4.56; N 14.36. $C_{20}H_{18}N_4O_4$. Calculated, %: C 63.49; H 4.79; N 14.81.

1,3-Dimethyl-6-(2-N-methylanilinovinyl)-5-nitropyrimidine-2,4(1H,3H)-dione (2e). A mixture of compound **1** (2.5 g, 12.6 mmol), N-methylaniline (4.2 g, 39 mmol), and triethyl orthoformiate (25 ml) was boiled for 24 h, after which the excess of the ortho ester was distilled over ~2 h with continued heating. After 2 h the orange-red crystals were filtered off and washed with 5-10 ml of alcohol. Yield 2.2 g (55%); mp 194-195°C (dioxane). IR spectrum, cm^{-1}: 1705, 1640 (CO). ^1H NMR spectrum (DMSO-d_6), ppm: 7.42 (2H, m, C_6H_5, *m*-H); 7.33 (1H, d, J_{trans} = 13.41 Hz, CH=CH–N); 7.17 (3H, m, C_6H_5, *o*- and *p*-H); 5.34 (1H, d, J = 13.41 Hz, CH=CH–N); 3.44 (3H, s, 1-CH_3); 3.34 (3H, s, 3-CH_3); 3.20 (3H, s, N(C_6H_5)CH_3). Found, %: C 56.84; H 5.23; N 17.62. $C_{15}H_{16}N_4O_4$. Calculated, %: C 56.96; H 5.10; N 17.71.

1,3-Dimethyl-6-(2-N-benzylanilinovinyl)-5-nitropyrimidine-2,4(1H,3H)-dione (2f). The compound was obtained similarly to compound **2e** from the substituted uracil **1** (2.5 g, 12.6 mmol), of N-benzylaniline (7.16 g, 39 mmol), and triethyl orthoformiate (25 ml). Yield 2.62 g (53%); mp 189-191°C (dioxane). IR spectrum, cm^{-1}: 1705, 1657 (CO). ^1H NMR spectrum ($CDCl_3$), ppm: 7.46 (1H, d, J_{trans} = 13.40 Hz, CH=CH–N); 7.44-7.13 (10H, m, 2 × C_6H_5); 4.97 (2H, s, CH_2); 4.74 (1H, d, J = 13.40 Hz, CH=CH–N); 3.32 (3H, s, 1-CH_3); 3.03 (3H, s, 3-CH_3). Found, %: C 64.53; H 5.36; N 14.62. $C_{21}H_{20}N_4O_4$. Calculated, %: C 64.28; H 5.14; N 14.28.

1,4-Bis[2-(1,3-dimethyl-5-nitro-2,4-dioxo-6-pyrimidyl)vinyl]piperazine (2g). A mixture of compound **1** (2 g, 10 mmol), piperazine (1.29 g, 16 mmol), and triethyl orthoformiate (10 ml) was boiled for 1 h 40 min. After cooling, ethanol (10 ml) was added, and the orange crystals of the product **2g** were filtered off and washed with alcohol (5 ml). Yield 1.78 g (71%); mp 291-293°C (DMSO). IR spectrum, cm^{-1}: 1697, 1632 (CO). ^1H NMR spectrum (DMSO-d_6); ppm: 6.98 (2H, d, J_{trans} = 13.18 Hz, 2 × CH=CH–N); 5.08 (2H, d, J = 13.18 Hz, 2 × CH=CH–N); 3.43 (8H, s, 4 × CH_2); 3.38 (6H, s, 1-CH_3); 3.16 (6H, s, 3-CH_3). Found, %: C 47.84; H 4.92; N 22.36. $C_{20}H_{24}N_8O_8$. Calculated, %: C 47.62; H 4.80; N 22.21.

5-Nitro-6-(2-morpholinovinyl)pyrimidine-2,4(1H,3H)-dione (2h). The compound was obtained similarly to compound **2c** from 5-nitro-6-methyluracil (2 g, 11.7 mmol), morpholine (3.05 g, 35 mmol), and triethyl orthoformiate (23 ml). After cooling the product was filtered off and washed with dimethyl sulfoxide and with ethanol. Yield 2.1 g (67%), and the product formed yellow crystals decomposing at 290-295°C (DMSO). IR spectrum, cm^{-1}: 3140 (br, NH); 1721, 1608 (br, CO, C=C). ^1H NMR spectrum (DMSO-d_6), ppm: 11.08 (1H, s, 1-NH); 10.77 (1H, br. s, 3-NH); 8.01 (1H, d, J_{trans} = 1.14 Hz, CH=CH–N); 5.48 (1H, d, J = 13.14 Hz, CH=CH–N); 3.65 (4H, t, 2'- and 6'-CH_2); 3.40 (4H, t, 3'- and 5'-CH_2). Found, %: C 44.97; H 5.06; N 21.03. $C_{10}H_{12}N_4O_5$. Calculated, %: C 44.78; H 4.51; N 20.89.

1,3-Dimethyl-6-(2-morpholinovinyl)pyrimidine-2,4(1H,3H)-dione (2i). The compound was obtained similarly to compound **2c** from 1,3,6-trimethyluracil (1.8 g, 11.7 mmol), morpholine (3.05 g, 35 mmol), and triethyl orthoformiate (23 ml). Yield 1.1 g (37%), and the product formed light-yellow needle crystals melting at 181-182°C (isopropyl alcohol). IR spectrum, cm^{-1}: 1665, 1616 (CO). ^1H NMR spectrum ($CDCl_3$), ppm: 6.84 (1H, d, J_{trans} = 13.02 Hz, CH=CH–N); 5.58 (1H, s, 5-H); 4.85 (1H, d, J = 13.02 Hz, CH=CH–N); 3.74 (4H, t, 2'- and 6'-CH_2); 3.39 (3H, s, 1-CH_3); 3.30 (3H, s, 3-CH_3); 3.19 (4H, t, 3'- and 5'-CH_2). Found, %: C 57.24; H 6.84; N 16.34. $C_{12}H_{17}N_3O_5$. Calculated, %: C 57.36; H 6.82; N 16.72.

1,3-Dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (3). A. To a solution of compound **2c** (6.7 g, 22.6 mmol) in acetic acid (83 ml), heated to 70-80°C, zinc dust (14.5 g) was added in portions with stirring while preventing excessive boiling. The mixture was then stirred at 85-95°C for 30 min, and the zinc salts that separated on cooling were filtered off and washed with 15-20 ml of acetic acid. The filtrate was diluted with four times the volume of water and extracted with chloroform (5 × 15 ml). The extract was washed with a saturated aqueous solution of sodium bicarbonate and dried with anhydrous sodium sulfate. The chloroform was distilled, and the residue was crystallized from ethanol. Compound **3** (2.37 g, 71%) was obtained. The product is identical in all its physicochemical characteristics with a previously obtained sample [3].

B. Compound **3** was obtained similarly from enamine **2b** (16.73 g, 57 mmol), acetic acid (76 ml), and zinc dust (27 g). Yield 6.92 g (67%).

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