Transformations of 5-Diazo Derivatives of 1,3-Dimethyl-6-hydrazinouracil: New Synthetic Approaches to Novel Pyrimidine Derivatives

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1,3-Dimethyl-6-hydrazinouracil **1** gives hydrazones **2** with the corresponding aldehydes. Heating of 6-hydrazinouracil **1** in ethanol in the presence of hydrochloric acid results in the formation of *N*^{1},*N*^{2}-bis(1,3-dimethyl-2,6-dioxopyrimid-4-yl)hydrazine **3**, which gives the diazo derivative **4** on treatment with 2,4-diazido-6-cyanomethoxy-*s*-triazine in DMSO in the presence of triethylamine at room temperature. 5-Diazo derivatives **5** (obtained under similar conditions from reactions between hydrazones **2** and the same 2,4-diazido-6-cyanomethoxy-*s*-triazine) are subsequently converted into triazolo[4.5-*d*]pyrimidines **6** in nearly quantitative yields after a short period of heating. Hydrazine **1** is transformed into the 2,4,7,9-tetramethyl-1,2,3,4,7,8,9,10-octahydropyrimido[4,5-*c*]pyridazino[3,4-*d*]pyrimidin-1,3,8,10-tetrone **7** under diazo-transfer conditions.

Hydrazinouracils possessing a nitrogen function at the C-5 position are known to be starting materials for the synthesis of various pyrimido-annelated heterocyclic systems, including pyrimidotriazine antibiotics (*e.g.* fervenulin, reumicin, toxoflavin, MSD-92) and their derivatives.[1] However, no data concerning methods of syntheses and properties of 5-diazo-6-hydrazinouracils have so far been reported in the literature. Meanwhile, these compounds are of interest in themselves and seem to be suitable starting materials for new syntheses.

In order to introduce the diazo function into the uracil ring we used the diazo-transfer reaction; 2,4-diazido-6-cyanomethoxy-*s*-triazine was employed as a donor of the diazo group.[2]

Diazouracils were derived from 1,3-dimethyl-6-hydrazinouracil **1**[3] and its hydrazones **2a–c** obtained by reactions with the corresponding aldehydes[†] (Scheme 1).

Another subject of our investigation was *N*^{1},*N*^{2}-bis(1,3-dimethyl-2,6-dioxopyrimid-4-yl)hydrazine **3**, an original synthesis of which has been developed in the course of our studies.[‡] Thus, heating of hydrazine **1** in ethanol in the presence of hydrochloric acid resulted in the formation of hydrazine **3** as a major product together with a small amount (4–5%) of 1,3-dimethylbarbituric acid. Elemental analyses and ^{1}H NMR data for compound **3** are in full agreement with the suggested structure. In the ^{1}H NMR spectrum of **3** measured in [^{2}H$_6$]DMSO the resonance of the N–CH$_3$ groups appear as singlets at 3.15 and 3.39 ppm, the H-5 proton resonates at 4.90 ppm and the NH-group signal was recorded at 9.08 ppm.

Table 1 Some characteristics of diazo derivatives **4**, **5a–c** and their cyclization products.

Compounds	M.p./°C	IR spectrum (γ_{N_2}/cm^{-1})
4	240–242	2110; 2130
5a	216–218[a]	2120
5b	222–224[a]	2120
5c	180–182[a]	2100
6a	275–277	–
6b	260–262	–
6c	268–270	–

[a] Temperature of cyclization of **5** into **6**.

The reaction of hydrazine **3** with 2,4-diazido-6-cyanomethoxy-*s*-triazine in the presence of triethylamine proceeded smoothly at room temperature and resulted in the formation of the diazo derivative **4**.[§] Diazo derivatives **5** were obtained under similar conditions by reactions between hydrazones **2** and the same 2,4-diazido-6-cyanomethoxy-*s*-triazine.[¶]

From the absence of H-5 resonance signals due to the uracil fragment in the ^{1}H NMR spectra of diazo compounds **4** and **5** it is clear that introduction of the diazo group occurs at the C-5 position. Absorption bands for the diazo group (γ_{N_2}) in the region of 2200–1900 cm^{-1} are available in the infrared spectra of compounds **4** and **5** measured in vaseline oil.

Compounds **5** were found to be converted into triazolopyrimidines **6**[*] in nearly quantitative yields without changes in the elemental composition of the molecules. The reactions were carried out on short heating of the reactants either in DMF solution or without any solvent until the reaction mixture became colourless. In the IR spectra of compounds **6** in vaseline oil no absorption was observed in the region of 2200–1900 cm^{-1}. Although cyclization of α-diazoimines into triazoles is a well-known reaction,[4] transformations of 5-diazo derivatives of 6-hydrazinouracil into the triazolopyrimidines have never been observed previously.

[†] A typical procedure for the synthesis of hydrazones **2a–c**. Equimolar amounts of 1,3-dimethyl-4-hydrazinopyrimidin-2,6-dione and the corresponding aldehyde were suspended in 50% aqueous ethanol. The reaction mixture was allowed to reflux for 5 min, cooled to room temperature and the precipitate obtained was filtered off. The analytically pure compounds **2a–c** were obtained by recrystallization from DMF in 80–85% yields. Melting points/°C: **2a** 266–268; **2b** 278–280; **2c** 270–272. ^{1}H NMR ([^{2}H$_6$]DMSO) for **2a**: δ 3.2 (3H, s, NMe), 3.4 (3H, s, NMe), 3.8 (3H, s, OMe), 5.5 (1H, s, C$_{(5)}$–H), 7.3 (4H, dd, Ph), 8.3 (1H, s, N=CH), 10.1 (1H, s, NH); **2b** ([^{2}H$_6$]DMSO): δ 3.2 (3H, s, NMe), 3.4 (3H, s, NMe), 5.6 (1H, s, C$_{(5)}$–H), 8.1 (4H, dd, Ph), 8.4 (1H, s, N=CH), 10.8 (1H, s, NH).

[‡] A typical procedure for the synthesis of *N*^{1},*N*^{2}-bis(1,3-dimethyl-4-hydrazino)pyrimidin-2,6-dione **3**. 1,3-Dimethyl-4-hydrazinopyrimidin-2,6-dione (0.8 g, 4 mmol) was heated in ethanol with 0.3 ml of hydrochloric acid for 10 min. The precipitate obtained was then filtered off from hot ethanol. The analytically pure compound **3** was obtained by reprecipitation with water from DMSO solution. Yield 44%; m.p. 270–272 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) for **3**: δ 3.3 (6H, s, NMe), 3.4 (6H, s, NMe), 5.0 (2H, s, C$_{(5;5')}$–H), 9.1 (2H, s, NH–NH).

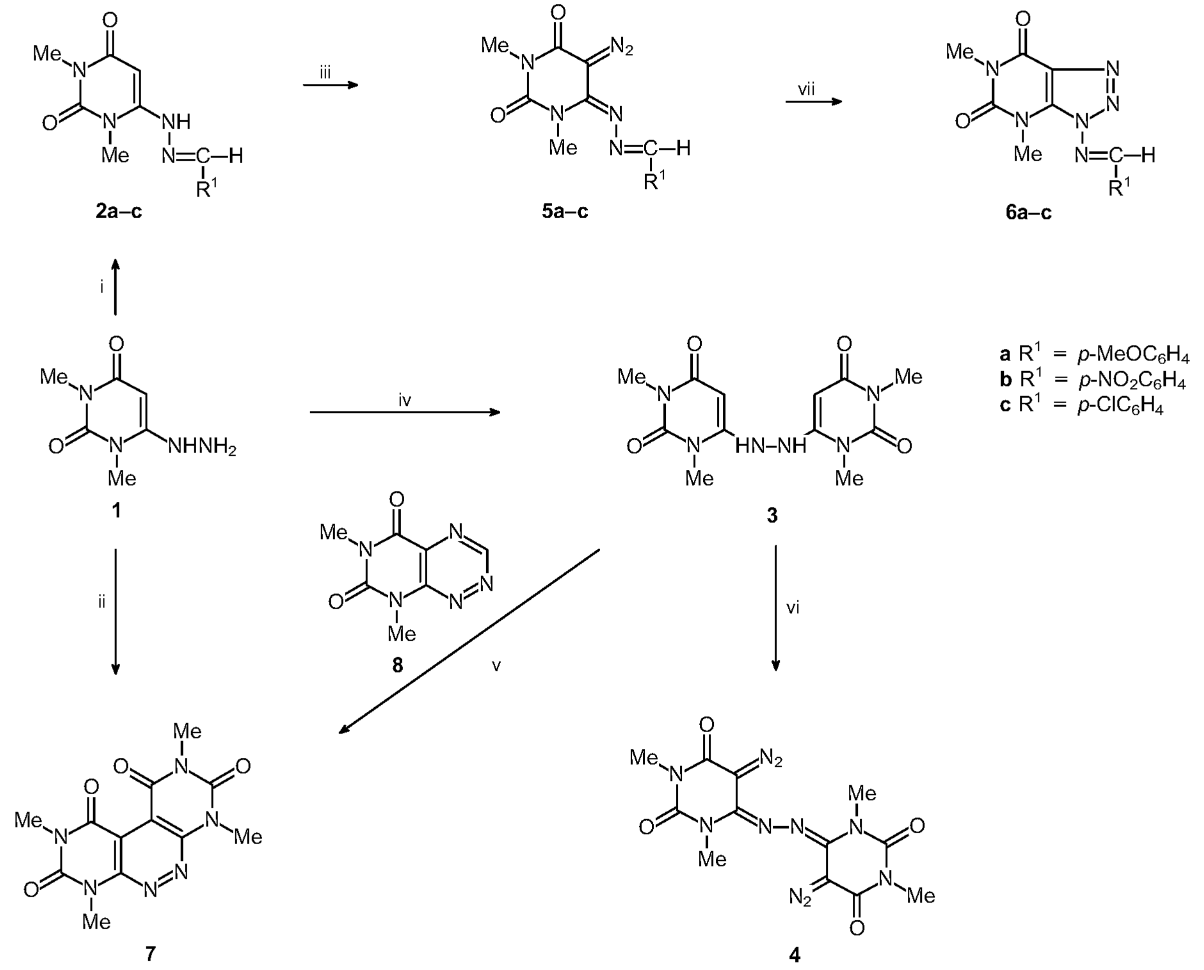
[§] A typical procedure for the synthesis of *N*^{1},*N*^{2}-bis(1,3-dimethyl-4-hydrazino-5-diazo)pyrimidin-2,6-dione **4**. 2,4-Diazido-6-cyanomethoxy-*s*-triazine (0.1 g) and 0.3 ml of triethylamine were added to a solution of *N*^{1},*N*^{2}-bis(1,3-dimethyl-4-hydrazino)pyrimidin-2,6-dione **3** (0.85 g, 3 mmol) in 10 ml of DMSO. The reaction mixture was kept at room temperature for 2 h and the resulting precipitate was filtered off. The analytically pure compound **4** was obtained by recrystallization from DMF in 65% yield.

CAUTION! 2,4-Diazido-6-cyanomethoxy-*s*-triazine and some other azidotriazines are notoriously unstable and explosive.

[¶] A typical procedure for the synthesis of 5-diazo-6-hydrazino derivatives of 1,3-dimethyluracil **5a–c**. Equimolar amounts of the corresponding hydrazones **2a–c**, 2,4-diazido-6-cyanomethoxy-*s*-triazine and triethylamine were dissolved in DMF at room temperature. Then the reaction mixture was stirred for 5–10 min and the precipitate obtained was filtered off, yields 65–70% (Table 1).

^{1}H NMR ([^{2}H$_6$]DMSO) for **5a**: δ 3.4 (3H, s, NMe), 3.5 (3H, s, NMe), 3.9 (3H, s, OMe), 7.3 (4H, dd, Ph), 8.2 (1H, s, N=CH); **5b** ([^{2}H$_6$]DMSO): δ 3.4 (3H, s, NMe), 3.5 (3H, s, NMe), 8.0 (4H, dd, Ph), 8.4 (1H, s, N=CH).

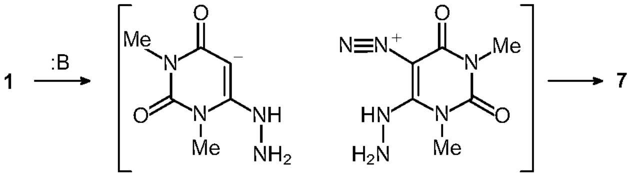
[*] A typical procedure for the synthesis of triazolo[4,5-*d*]pyrimidines **6a–c**. A saturated solution of the corresponding 5-diazo derivative **5a–c** was heated for 5–10 min. The reaction mixture was then cooled and the precipitate obtained was filtered off, yield 80–85% (Table 1). Triazolopyrimidines **6a–c** were also obtained in quantitative yields on heating the corresponding 5-diazo derivatives without solvent until the crystals became colourless.



Scheme 1 *Reagents and conditions*: i, EtOH (50%), Δ, R^{1}CHO; ii, DMSO, Het-N$_3$ (2,4-diazido-6-cyanomethoxy-*s*-triazine), :B (NEt$_3$); iii, Het-N$_3$, :B, DMF; iv, EtOH, H$^+$, Δ; v, EtOH, H$^+$, Δ; vi, Het-N$_3$, :B; vii, Δ, DMF.

In the course of our studies on the diazo-transfer reaction an unusual transformation of hydrazine **1** into the previously described[5] 2,4,7,9-tetramethylpyrimidin-1,3,8,10-tetrone **7**[+] was found. Compound **7** was also obtained on heating of hydrazine **3** with antibiotic fervenulin **8** in ethanol.

In conclusion, from the above data we assume that the formation of product **7** proceeds *via* interaction of intermediates **1A** and **1B**:



1A **1B**

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[+] A typical procedure for the synthesis of 2,4,7,9-tetramethyl-1,2,3,4,7,8,9,10-octahydropyrimido[4,5-*c*]pyridazino[3,4-*d*]pyrimidin-1,3,8,10-tetrone **7**. 1,3-Dimethyl-4-hydrazinopyrimidin-2,6-dione (1.7 g, 0.02 mol) was refluxed in 10 ml of ethanol with 1.5 ml of hydrochloric acid and fervenulin (2.9 g, 0.01 mol) for 1 h. The reaction mixture was then cooled and the precipitate obtained was filtered off, yield 25–30%, m.p. 347–349 °C.
An alternative procedure for the synthesis of **7** was as follows: 2,4-diazido-6-cyanomethoxy-*s*-triazine (1.1 g, 0.005 mol) and 0.5 ml of triethylamine were added to a solution of 1,3-dimethyl-4-hydrazinopyrimidin-2,6-dione **1** (0.85 g, 0.005 mol) in 10 ml of DMSO. The reaction mixture was kept at room temperature for 5–6 h and the resulting precipitate was filtered off and recrystallized from DMF, yield 5%.