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Syntheses with Nitriles, XCV [1]: Deamination of Cytosine Derivatives

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Summary. Treatment of 2-formyl-3-dimethylamino-propenenitrile (**1a**) and 2-ethoxycarbonyl-3-dimethylamino-propenenitrile (**1b**), resp., with substituted ureas led to the 2-cyano-3-ureidoacrylates **2**, which can be cyclized under alkaline conditions to give 5-formyl-5-cyano-, and 5-alkoxycarbonyl-2-oxopyrimidine derivatives **3**, **6**, and **7**. Reaction of **3** with isopentylnitrite gave a mixture of the deaminated and oxidized product **4** and the oxo derivative **5**, which was acetalized during the separation step. Similar reaction with the alkoxycarbonyl derivatives **7** led to the formation of 1-alkyl-5-alkoxycarbonyl-pyrimidine-2,6-diones **8a–d**.

Keywords. 2,6-Dihydroxypyrimidines; Pyrimidinones; Pyrimidine-2,6-diones; Cytosine.

Synthesen mit Nitrilen, 95. Mitt. [1]**: Deaminierung von Cytosinderivaten**

Zusammenfassung. Die Reaktion von 2-Formyl-3-dimethylamino-propennitril (**1a**) und 2-Ethoxycarbonyl-3-dimethylamino-propennitril (**1b**) mit substituierten Harnstoffen führte zur Bildung der 2-Cyan-3-ureidoacrlate **2**, welche unter alkalischen Bedingungen zu den 5-Formyl-, 5-Cyan- oder 5-Alkoxycarbonyl-2-oxopyrimidinen **3**, **6** bzw. **7** cyclisiert werden konnten. Reaktion von **3** mit Isopentylnitrit ergab eine Mischung aus deaminiertem und zugleich oxidiertem Produkt **4** sowie dem Oxoderivat **5**, welches während der Säulentrennung auf Kieselgel zusätzlich acetalisiert worden war. Die ähnliche Reaktion mit den Alkoxycarbonyl-Derivativen **7** führte zur Bildung der 1-Alkyl-5-alkoxycarbonyl-pyrimidin-2,6-dione **8a–d**.

Introduction

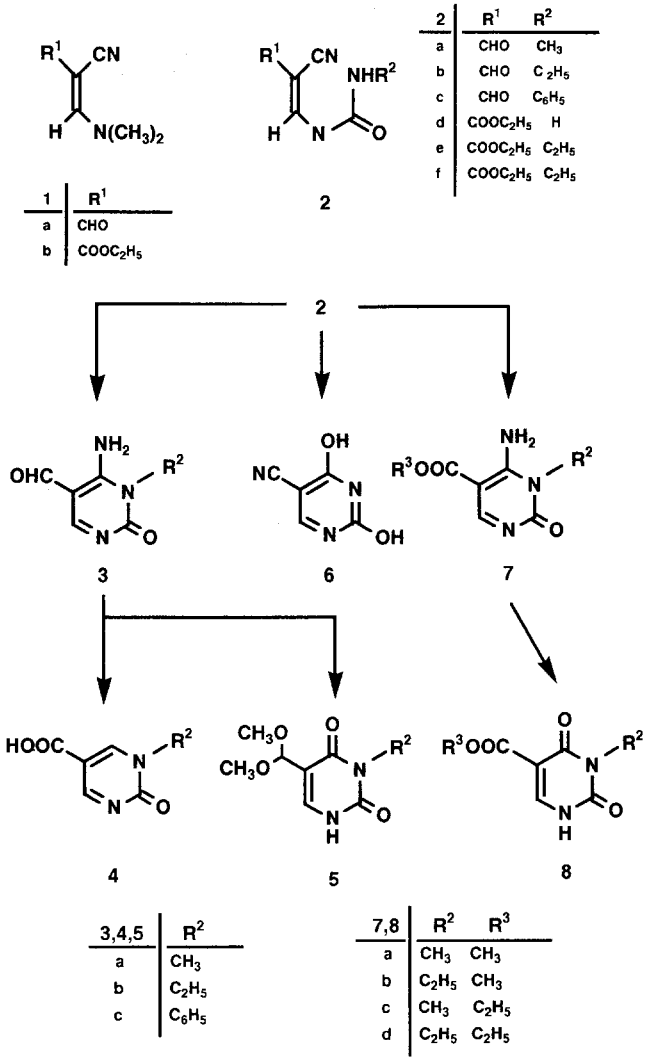
Pyrimidine derivatives are of special importance because of their versatile biological activities [2–5] due to their occurrence in natural products like nucleic acids and vitamine B_1 [6]. Cytosine derivatives can be used as therapeutic agents for the treatment of AIDS [7], and some fluoro derivatives exhibit antitumor activities. There are also some technical applications like the use in liquid crystal composition [8].

In this paper, deamination reactions of 4-amino-5-formyl- and 4-amino-5-carboyxyalkyl-pyrimidine-2-one derivatives, obtained from the well known 2-formyl-3-dimethylamino-propenenitrile (**1a**) and 2-ethoxycarbonyl-3-dimethylamino-propenenitrile (**1b**), are described.

Results and Discussion

1a and **1b** can easily be synthesized by condensation of cyanoacetaldehyde and cyano acetate with dimethylformamide-dimethylacetal [9, 10]. In a previous paper of this series, we reported the synthesis of 4-amino-5-formyl-2-oxo-pyrimidine derivatives **3** by reaction of **1a** with substituted ureas and further ring closure [11]. Similar reaction of **1b** with substituted ureas in acidic medium yielded the ureido-acrylates **2d–f**, which can be cyclized under alkaline conditions to give 1-alkyl-6-amino-5-alkoxycarbonyl-pyrimidine-2(1*H*)ones (**7a–d**). Depending on the alcohol used for that reaction, either methyl or ethyl carboxylates could be obtained. In the case of the N-unsubstituted derivative **2d** 5-cyano-2, 4-dihydroxy pyrimidine (**6**) could be isolated. The open chain intermediates **2d–f** are obtained as mixtures of *E*/*Z* isomers, the proportion of which could be determined by ^{1}H NMR spectroscopy.

In our studies we tried to deaminate the 4-aminopyrimidines **3** and **7** with the use of isopentylnitrite in dimethylformamide according to *Doyle et al.* [12], applicated



Scheme 1

for the deamination of substituted anilines. In the case of **3a–c** a mixture of two compounds was isolated which could be separated on silica with a mixture of chloroform and methanol. One compound could be identified as the deaminated product **4**. The treatment, however, also led to the oxidation of the aldehyde function to a carboxylic group. The other product was identified as the 5-dimethoxymethyl-pyrimidine-2,6-dione derivative **5**. In this case, the amino group was converted into a hydroxy function, and furthermore the product was acetalized during the separation process catalyzed by silica gel. Similiarly, the reaction of **7** with isopentylnitrite did not lead to the deaminated products, but to the formation of the corresponding 4-oxo derivatives **8**.

Experimental

Melting points are uncorrected (Büchi-500). IR-spectra were recorded on a Perkin-Elmer spectrophotometer 298 (KBr pellet) and ^{1}H NMR spectra on a Varian 360 AM and Gemini 200 instrument (reference: tetramethylisilane). Column chromatography was carried out using E. Merck silica gel G (partical size 70–230 mesh ASTM).

General procedure for the preparation of ethyl 2-cyano-3-ureidoacrylates (**2d–f**)

A mixture of **1b** (10 mmol) and the corresponding urea (10 mmol) in ethanol (20 ml) and conc. HCl (3 ml) was refluxed for 36 h, cooled, and the solvent removed under reduced pressure. The semi-solid mass was column chromatographed using methanol:chloroform (5:95 v/v) on silica gel-G. For physical and spectroscopic data see Tables 1 and 2.

Preparation of 5-carboxy-1-alkyl/aryl-pyrimidine-(1H)-2-ones (**4a–c**) *and 1-alkyl/aryl-5-dimethoxymethyl-pyrimidine-(1H)-2,6-diones* (**5a–c**)

To a rapidly stirred solution of **3** in anhydrous N, N-dimethylformamide (5 ml) maintained at 65 °C, a solution of isopentylnitrite (15 mmol) in anhydrous *DMF* (5 ml) was added over a period of 10 min. The reaction mixture was stirred for 30 min and concentrated. The separated solid was chromatographed using silica gel-G and chloroform:methanol (95:5 v/v) as solvent. For physical and spectroscopic data see Tables 3 and 4.

5-Cyano-2,4-dihydroxy pyrimidine (**6**)

To a solution of **2d** (0.36 g, 2 mmol) in methanol, sodium methoxide prepared from sodium (0.05 g, 2 mg-atom) in methanol (5 ml) was added and the reaction mixture was refluxed for 1.5 h. The solvent

Table 1. Yield and melting points of ethyl 2-cyano-3-ureidoacrylates **2d–f**

	Yield (%)	M.p. (°C)	Molecular formula[a]	Molecular weight
2d	50	214 (Ref. [13]: 215)	$C_7H_9N_3O_3$	183.2
2e	50	153 (Ref. [14]: 155)	$C_8H_{11}N_3O_3$	197.2
2f	55	156 (Ref. [13]: 156)	$C_9H_{13}N_3O_3$	211.2

[a] Elemental analyses (C, H, N) are in agreement with calculated values

was removed under reduced pressure and the soild obtained recrystallized from methanol; 73%, m.p. 296 °C dec. (Ref. [15]: 295 °C dec.). IR: $\nu = 3580, 2230, 1625\,cm^{-1}$; ^1H NMR (*DMSO*-d_6): $\delta = 8.0$ (s, =CH), 10.1 (s br, 2H, OH) ppm.

General procedure for the preparation of 1-alkyl-6-amino-5-alkoxycarbonyl pyrimidine-2-(1H)-ones (**7a–d**)

To a solution of sodium methoxide in methanol, prepared from sodium (0.02 g, 1 mg-atom) and methanol (5 ml) or sodium ethoxide prepared from sodium (0.2 g, 1 mg-atom) and ethanol (5 ml),

Table 2. IR and ^1H NMR data of ethyl 2-cyano-3-ureidoacrylates **2d–f**

	Ratio of isomers	IR (KBr) $\nu(cm^{-1})$	^1H NMR (*DMSO*-d_6) δ (ppm)
2d	20:80	3360, 3200 (NH) 2220 (CN), 1750 (C=O), 1680 (C=O)	major isomer: 1.25 (t, $J = 7.5$ Hz, 3H, CH_3), 4.20 (q, $J = 7.5$ Hz, 2H, CH_2), 7.45 (s, br, 2H, NH_2), 8.45 (d, $J = 13$ Hz, 1H, =CH), 10.35 (d, $J = 13$ Hz, 1H, NH) minor isomer: 1.27 (t, $J = 7.5$ Hz, 3H, CH_3), 3.95 (q, $J = 7.5$ Hz, 2H, CH_2), 7.65 (s, br, 2H, NH_2), 8.15 (d, $J = 13$ Hz, 1H, =CH), 10.60 (d, $J = 13$ Hz, 1H, NH)
2e	85:15	3360 (NH), 2210 (CN), 1730 (C=O), 1680 (C=O)	major isomer: 1.25 (t, $J = 7.5$ Hz, 3H, CH_3), 2.8 (d, $J = 6$ Hz, 3H, CH_3), 4.2 (q, $J = 7.5$ Hz, 2H, CH_2), 7.1 (q unresolved, 1H, NH), 8.45 (d, $J = 13$ Hz, 1H, =CH), 10.5 (d, $J = 13$ Hz, 1H, NH) minor isomer: 1.28 (t, $J = 10$ Hz, 3H, CH_3), 2.82 (d, $J = 6$ Hz, 3H, CH_3), 4.25 (q, $J = 10$ Hz, 2H, CH_2), 7.15 (q unresolved, 1H, NH), 8.25 (d, $J = 13$ Hz, 1H, =CH), 10.63 (d, $J = 13$ Hz, 1H, NH)
2f	90:10	3370, 3320 (NH), 2225 (CN), 1730 (C=O), 1680 (C=O)	major isomer: 1.1 (t, $J = 7.5$ Hz, 3H, CH_3), 1.2 (t, $J = 7.5$ Hz, 3H, CH_3), 3.18 (m, 2H, CH_2), 4.2 (q, $J = 7.5$ Hz, 2H, CH_2), 7.2 (q unresolved, 1H, NH), 8.2 (d, $J = 12.5$ Hz, 1H, =CH), 10.5 (d, $J = 12.5$ Hz, 1H, NH) minor isomer: 1.12 (t, $J = 7.5$ Hz, 3H, CH_3), 1.25 (t, $J = 7.5$ Hz, 3H, CH_3), 3.2 (m, 2H, CH_2), 4.25 (q, $J = 7.5$ Hz, 2H, CH_2), 7.45 (q unresolved, 1H, NH), 8.17 (d, $J = 12.5$ Hz, 1H, =CH), 9.3 (s br, 1H, NH)

Table 3. Yield and melting points of **4a–c** and **5a–c**

	Yield (%)	M.p. (°C)	Molecular formula[a]	Molecular weight
4a	62	221	$C_6H_6N_2O_3$	154.1
4b	55	179	$C_7H_9N_3O_3$	183.1
4c	56	223	$C_{11}H_8N_2O_3$	216.2
5a	20	155	$C_8H_{12}N_2O_4$	200.2
5b	15	91	$C_9H_{13}N_2O_4$	213.2
5c	10	55	$C_{13}H_{14}N_2O_4$	262.3

[a] See footnote of Table 1

Table 4. IR and ^1H NMR data of **4a–c** and **5a–c**

	IR (KBr) $\nu(cm^{-1})$	^1H NMR δ (ppm)
4a	3120 (OH), 1740 (C=O), 1680 (C=O), 1620 (C=N)	*DMSO*-d_6; 3.18 (s, 3H, CH_3), 8.26 (s, 1H, =CH), 9.81 (s, 1H, =CH), 12.2 (s, br, 1H, –OH)
4b	3250, 2800 (OH), 1740 (C=O), 1680 (C=O), 1620 (C=N)	*DMSO*-d_6; 1.16 (t, $J = 7.5$ Hz, 2H, CH_2), 3.85 (q, $J = 7.5$ Hz, 2H, CH_2), 8.18 (s, 1H, =CH), 9.82 (s, 1H, =CH), 12.8 (s, br, 1H, OH)
4c	3300, 2850 (OH), 1730 (C=O), 1680 (C=O), 1620 (C=N)	*DMSO*-d_6; 7.25–7.6 (m, 5H, aromatic protons), 8.3 (s, 1H, =CH), 9.83 (s, 1H, =CH), 12.2 (s, br, 1H, =CH)
5a	3150, 2950 (NH), 1740 (C=O), 1670 (C=O), 1615 (C=N)	$CDCl_3$; 3.35 (s, 3H, CH_3), 3.42 (s, 6H, OCH_3), 5.35 (s, 1H, CH), 7.45 (d, $J = 6$ Hz, 1H, =CH), 9.7 (d, $J = 6$ Hz, 1H, NH)
5b	3150, 2950 (NH), 1730 (C=O), 1665 (C=O), 1620 (C=N)	$CDCl_3$; 1.1 (t, $J = 7.5$ Hz, 3H, CH_3), 3.25 (s, 6H, OCH_3), 3.85 (q, $J = 7.5$ Hz, 2H, CH_2), 5.25 (s, 1H, CH), 7.35 (d, $J = 6$ Hz, 1H, =CH), 10.5 (d, $J = 6$ Hz, 1H, NH)
5c	3150, 2950 (NH), 1720 (C=O), 1670 (C=O), 1620 (C=N)	$CDCl_3$; 3.4 (s, 6H, OCH_3), 5.28 (s, 1H, CH), 7.25–7.55 (m, 6H, aromatic protons and =CH), 10.15 (d, $J = 6$ Hz, NH)

Table 5. Yield and melting points of **7a–d**

	Yield (%)	M.p. (°C)	Molecular formula[a]	Molecular weight
7a	76	212	$C_7H_9N_3O_3$	183.2
7b	50	217	$C_8H_{11}N_3O_3$	197.2
7c	79	233 (Ref. [14]: 234)	$C_8H_{11}N_3O_3$	197.2
7d	55	201 (Ref. [14]: 201)	$C_9H_{13}N_3O_3$	211.2

[a] See footnote of Table 1

Table 6. IR and ^{1}H NMR data of the **7a–d**

	IR(KBr) ν(cm^{-1})	^{1}H NMR (*DMSO*-d$_6$) δ(ppm)
7a	3300, 3150 (NH), 1730 (C=O), 1660 (C=O), 1610 (C=N)	3.38 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 8.55 (s, 1H, =CH), 8.6–8.8 (s, br, 2H, NH_2)
7b	3300, 3150 (NH), 1730 (C=O), 1665 (C=O), 1620 (C=N)	1.15 (t, J = 7.5 Hz, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.8 (q, J = 7.5 Hz, 2H, CH_2), 8.45 (s, 1H, =CH), 8.5–8.7 (s, br, 2H, NH_2)
7c	3320 (NH), 1730 (C=O), 1675 (C=O), 1620 (C=N)	1.3 (t, J = 7.5 Hz, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.25 (d, J = 7.5 Hz, 2H, CH_2), 8.5 (s, 1H, =CH), 8.6–8.8 (s, br, 2H, NH_2)
7d	3300, 3100 (NH), 1730 (C=O), 1660 (C=O), 1620 (C=N)	1.25 (t, J = 7.5 Hz, 3H, CH_3), 1.38 (t, J = 7.5 Hz, 2H, CH_2), 4.25 (q, J = 7.5 Hz, 2H, CH_2), 8.55 (s, 1H, =CH), 8.65–8.8 (s, br, 2H, NH_2).

Table 7. Yield and melting points of **8a–d**

	Yield (%)	M.p. (°C)	Molecular formula[a]	Molecular weight
8a	50	239	$C_7H_8N_2O_4$	184.2
8b	48	228	$C_8H_{10}N_2O_4$	198.2
8c	46	220 (Ref. [16]: 221)	$C_8H_{10}N_2O_4$	198.2
8d	50	217 (Ref. [16]: 219)	$C_9H_{12}N_2O_4$	212.2

[a] See footnote of Table 1

Table 8. IR and ^{1}H NMR data of **8a–d**

	IR (KBr) ν(cm^{-1})	^{1}H NMR δ(ppm)
8a	3150–3200 (NH), 1755 (C=O), 1710–1690 (C=O), 1660 (C=O)	*DMSO*-d$_6$; 3.15 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 8.2 (d, 1H, =CH), 10.35 (d unresolved, 1H, NH).
8b	3100–3300 (NH), 1750 (C=O), 1695 (C=O), 1650 (C=O)	$CDCl_3$; 1.25 (t, J = 7.5 Hz, CH_3), 3.85 (s, 3H, OCH_3), 4.05 (q, J = 7.5 Hz, 2H, CH_2), 8.3 (d, J = 7 Hz, =CH), 10.35 (d, br, 1H, NH)
8c	3100–3300 (NH), 1750 (C=O), 1695 (C=O), 1650 (C=O)	*DMSO*-d$_6$; 1.25 (t, J = 7.5 Hz, 3H, CH_3), 3.15 (s, 3H, CH_3), 4.2 (q, J = 7.5 Hz, 2H, CH_2), 8.15 (d, J = 7.5 Hz, 1H, =CH), 11.85 (d, J = 7 Hz, 1H, NH)
8d	3100–3250 (NH), 1750 (C=O), 1695 (C=O), 1640 (C=O)	$CDCl_3$; 1.25 (t, J = 7.5 Hz, 3H, CH_3), 1.35 (t, J = 7.5 Hz, 2H, CH_2), 4.05 (q, J = 7.5 Hz, 2H, CH_2), 4.35 (q, J = 7.5 Hz, 2H, CH_2), 8.3 (d, J = 7 Hz, 1H, =CH), 10.35 (d unresolved, 1H, NH)

ethyl-2-cyano-3-ureidoacylate **2** (0.17 g, 1 mmol) in methanol/ethanol (15 ml) was added and refluxed for 1.5 h. The solvent was removed under reduced pressure to obtain a solid which was recrystallized from methanol. For physical and spectroscopic data see Tables 5 and 6.

General procedure for the preparation of 1-alkyl-5-methoxycarbonyl/5-ethoxycarbonyl-pyrimidine-2,6-diones (**8a–d**)

To a solution of **7** (1 mmol) in anhydrous dimethylformamide (3 ml) maintained at 65 °C, isopentylnitrite (1.5 mmol) in anhydrous *DMF* (3 ml) was added over 10 min. The mixture was stirred for 30 min. The solvent was removed under reduced pressure to get a solid which was chromatographed using silica gel-G and the solvent system methanol:chloroform (5:95 v/v). For physical and spectroscopic data see Tables 7 and 8.

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