

Convergent Domino *Knoevenagel* Hetero-*Diels–Alder* and Domino Oxidation Hetero-*Diels–Alder* Reactions Encountered in an Unexpected Formation of Novel 5-Aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and 5-Aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones

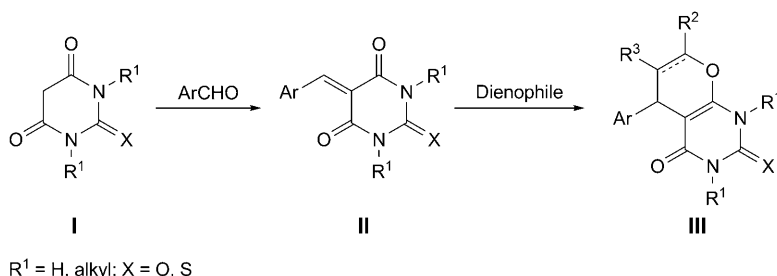
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Convergent domino *Knoevenagel* hetero-*Diels–Alder* and domino oxidation hetero-*Diels–Alder* reactions, in which both diene and dienophile are formed under the same reaction conditions *in situ*, are described for the first time, and their application is demonstrated by a one-pot synthesis of novel 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and 5-aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones.

Introduction. – Domino reactions involving hetero-*Diels–Alder* cycloaddition reaction constitute a powerful strategy for the synthesis of complex organic molecules [1]. Among them, the domino *Knoevenagel* hetero-*Diels–Alder* reaction [1b][2], in which a diene, generated from a 1,3-dicarbonyl compound and an aldehyde, reacts with a dienophile, *e.g.*, an enol ether [3a], alkene [2d][2e], alkyne [3b][3c], or enamine [3d], has been frequently applied for the synthesis of natural products and highly diversified molecules. Whereas, in such reactions, different substrates, *e.g.*, barbituric acids and *Meldrum's* acid, have been used for generating dienes, dienophiles have not been produced *in situ* but added as reagents. A domino process in which both the diene and the dienophile would be generated *in situ* under the same reaction conditions, and would subsequently react to give a hetero-*Diels–Alder* product, is a challenging concept, which, to the best of our knowledge, has not been encountered in domino sequences involving a hetero-*Diels–Alder* reaction.

5-Unsubstituted barbituric acids **I** undergo the *Knoevenagel* condensation with aldehydes to afford 5-ylidene derivatives **II** [4], which have been reported to react as dienes in a hetero-*Diels–Alder* reaction to give 6/7-substituted 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones or their 2-thioxo analogues **III** (X = S) [3] (*Scheme 1*). As fused uracils, these compounds have received considerable attention due to their biological effects, including antiviral [5], antibacterial [6], antifungal [7], and prostate-protective activities [8]. 6,7-Unsubstituted derivatives of **III** have not been obtained by cycloaddition so far. The development of new synthetic strategies for the synthesis of novel 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and their 2-thioxo analogs is, therefore, of significant relevance. 5-Arylidenebarbituric acid derivatives **II** obtained by *Knoevenagel* condensation can also be easily reduced at the exocyclic C=C bond [9], so they can be considered as models of redox coenzymes such

Scheme 1. *Synthesis of 5-Aryl-1H-pyrano[2,3-d]pyrimidine-2,4(3H,5H)-diones and Their 2-Thioxo Analogs via Consecutive Knoevenagel Condensation and Hetero-Diels–Alder Cycloaddition*

Results and Discussion. – In the course of our research on novel antibacterial compounds [12][13], we discovered an unexpected synthesis of novel 6,7-unsubstituted 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and their 2-thioxo analogues **3a–3l** in a catalyst-free, one-pot reaction, which was performed simply by heating barbituric or 2-thiobarbituric acid with a benzaldehyde derivative, **1a–1g**, in EtOH/H₂O¹). Application of microwave irradiation substantially reduced the reaction times (from 3 d to *ca.* 1–2 h) but did not significantly influence the reaction yields (*Table*). This is, to the best of our knowledge, the first domino *Knoevenagel* hetero-*Diels–Alder* reaction in which both diene and dienophile are formed *in situ*. The conversion in fact comprises two interconnected domino reaction sequences: *i*) a domino *Knoevenagel* hetero-*Diels–Alder* reaction, and *ii*) a domino oxidation hetero-*Diels–Alder* reaction, both converging in products **3a–3l** (*Scheme 2*). The sequences can thus be described as convergent domino *Knoevenagel* hetero-*Diels–Alder* and domino oxidation hetero-*Diels–Alder* reactions.

A proposed mechanism for the reaction of barbituric (= pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) or 2-thiobarbituric acid (= 2,3-dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione) (**2a** and **2b**, resp.) and substituted benzaldehydes **1a–1g** in EtOH/H₂O leading to 5-aryl-1*H*-pyrano[2,3-*d*]-pyrimidinones and 5-aryl-2,3-dihydro-2-thioxo-1*H*-pyrano-[2,3-*d*]pyrimidin-4(5*H*)-ones **3a–3l** is depicted in *Scheme 3*. First, *Knoevenagel* condensation of an aromatic aldehyde **1a–1g** with **2a** or **2b** affords a 5-benzylidenearbituric acid **A**, which, due to its readily reducible exocyclic C=C bond, is responsible for oxidation of EtOH to acetaldehyde (MeCHO) [10]. It is noteworthy that MeCHO enters the following reaction step in its enol form, **B** (R¹ = H). As a dienophile, it reacts with **A** in a hetero-*Diels–Alder* reaction to give, after elimination of H₂O from intermediate **C**, the fused products **3a–3l**. Alternatively, formation of ethyl vinyl ether, **B** (R¹ = Et) from MeCHO and EtOH, and elimination of EtOH from

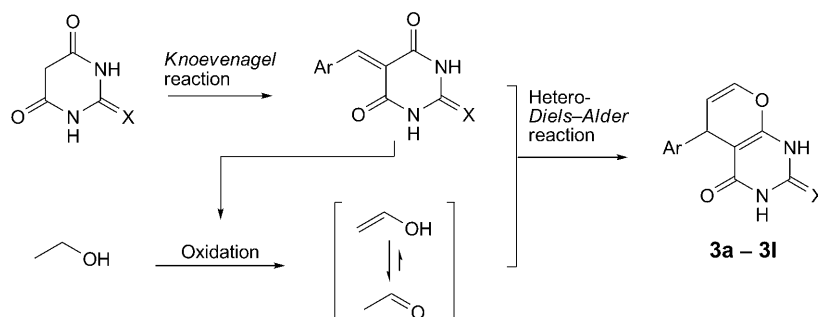
1) So far, only 6- and 7-substituted derivatives of **III** have been obtained by cycloaddition. Only two 6,7-unsubstituted derivatives of **III** ($R^1 = \text{Me}$, $R^2 = R^3 = \text{H}$, $\text{Ar} = \text{Ph}$ or $4\text{-MeO-C}_6\text{H}_4$) are known. They were obtained as side-products by elimination of a substituent at C(7) (see [3d]).

Table. Synthesis of 5-Aryl-1H-pyrano[2,3-d]pyrimidine-2,4(3H,5H)-diones and Their 2-Thioxo Analogs **3a–3l**^{a)}

Entry	1	R	2	X	Product	Yield [%] ^{b)}	
						Method A	Method B
1	1a	H	2a	S	3a	24	23
2	1b	3-NO ₂	2b	O	3b	56	35 ^{c)}
3	1b	3-NO ₂	2a	S	3c	34	33
4	1c	4-NO ₂	2b	O	3d	58	46
5	1c	4-NO ₂	2a	S	3e	58	40
6	1d	3-CN	2b	O	3f	58	57 ^{c)}
7	1d	3-CN	2a	S	3g	26	44
8	1e	4-CN	2b	O	3h	58	46
9	1e	4-CN	2a	S	3i	46	60
10	1f	4-COOH	2b	O	3j	44	42 ^{c)}
11	1f	4-COOH	2a	S	3k	20	27
12	1g	4-COOMe	2b	O	3l	28	30

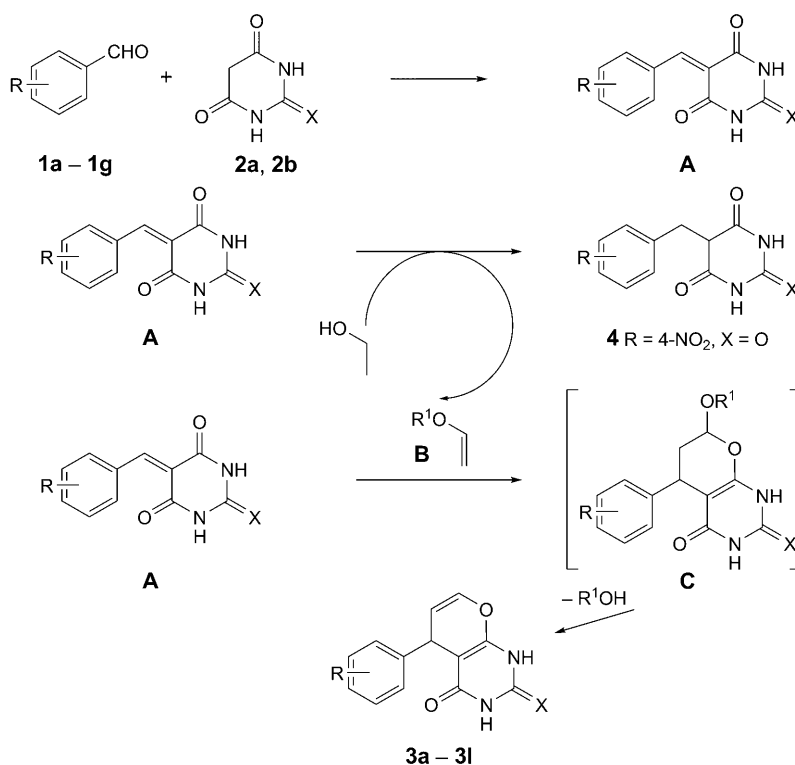
^{a)} Reaction conditions: **1** (1 mmol), **2** (1 mmol), and EtOH/H₂O 1:1, reflux, 3 d (*Method A*) or microwave irradiation: 120°, 30 W, 40 min (*Method B*). ^{b)} Yield of isolated pure product; yields were calculated considering that 100% yield corresponds to the conversion of 1 mmol of **1a–1g** to 0.5 mmol of **3a–3l**, which is in agreement with the reaction mechanism depicted in Scheme 3. ^{c)} Reaction time: 2 h.

Scheme 2. Formation of 5-Aryl-1H-pyrano[2,3-d]pyrimidine-2,4(3H,5H)-diones and Their 2-Thioxo Analogs by Convergent Domino Knoevenagel Hetero-Diels–Alder and Domino Oxidation Hetero-Diels–Alder Reactions

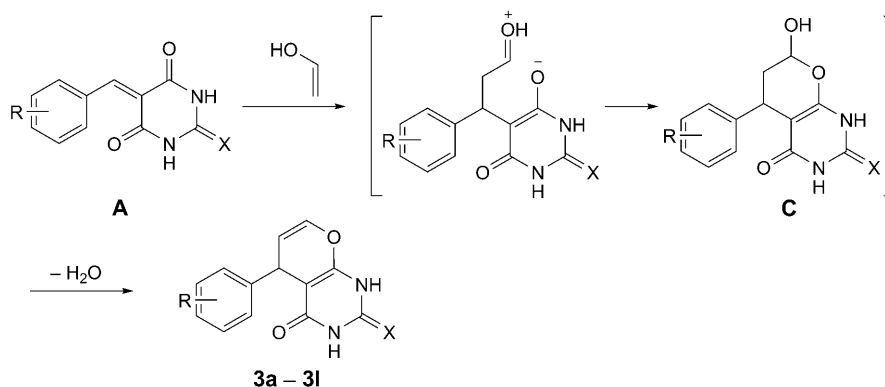


intermediate **C** could be anticipated. A formal domino *Knoevenagel* hetero-*Diels–Alder* reaction has been proposed previously for the reaction of ethyl vinyl ether with various benzaldehydes and 1,3-dimethylbarbituric acid [**3a**]. An alternative mecha-

Scheme 3. Mechanistic Proposal for the Synthesis of 5-Aryl-1H-pyrano[2,3-d]pyrimidinones and 5-Aryl-2,3-dihydro-2-thioxo-1H-pyrano[2,3-d]-pyrimidin-4(5H)-ones **3a–3l**



nistic explanation for the formation of **3a–3l** could be a *Michael* addition of the enol form of MeCHO at the 5-benzylidenebarbituric acid **A**, followed by the cyclization to **C** and subsequent elimination of H₂O (Scheme 4). Yields compiled in the Table were calculated considering that 100% yield corresponds to the conversion of 1 mmol of **1a–1g** to 0.5 mmol of **3a–3l**, which is in agreement with the described reaction mechanism. According to Yoneda *et al.* [10], the oxidizing ability of 5-benzylidenebarbituric acids depends on the electron density in the C=C bond and, hence, on the number and strength of electron-withdrawing substituents on the aromatic ring. This explains why the reaction proceeds well with nitro-, carboxy- and cyanobenzaldehydes, but not with 4-hydroxybenzaldehyde. Although oxidation of several alcohols with 5-arylidene-barbituric acids has been described [10], in our hands the reaction with other alcohols (PrOH, i-PrOH) was not successful, indicating that steric factors in the dienophile might play a role. To verify the proposed reaction mechanism, we heated 5-(4-nitrobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (**A**, R = 4-NO₂, X = O) in EtOH/H₂O and obtained the product **3d** in 30% yield, indicating that the *Knoevenagel* condensation indeed occurs first. To confirm that the oxidation of EtOH to MeCHO and the reduction of the exocyclic C=C bond of 5-arylidene-barbituric acids take place in the next step, we examined the reaction of 4-nitrobenzaldehyde and barbituric acid

Scheme 4. Alternative Mechanism for the Synthesis of **3a–3l**

(**2a**) in EtOH/H₂O. After filtering off the product **3d** from the mixture, the reduced derivative, 5-(4-nitrobenzyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**), was isolated from the mother liquid by column chromatography. The reaction gave identical results under Ar atmosphere, thus excluding a possible oxidation of EtOH²⁾ by atmospheric O₂. Finally, we sought to establish whether MeCHO reacts with 5-(4-nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**A**; R = 4-NO₂, X = O) in a hetero-*Diels–Alder* reaction. To this end, 4-nitrobenzaldehyde and barbituric acid (**2a**) were reacted in pure H₂O at 100° to give first 5-(4-nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**A**; R = 4-NO₂, X = O). After subsequent addition of MeCHO, crystals formed in the reaction mixture were filtered off and confirmed to be identical to product **3d**. The formation of **3d** from **1c**, **2a**, and MeCHO in the absence of EtOH thus excludes the intermediacy of ethyl vinyl ether (**B**; R¹ = Et). All these experiments support a three-component convergent domino reaction mechanism for the formation of 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidinones and 5-aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones **3a–3l**, comprising a hetero *Diels–Alder* reaction of 5-arylidene-barbituric acid **A** with the enol of MeCHO, both formed *in situ*, as proposed in Scheme 3.

Conclusions. – In conclusion, we have described the first convergent domino *Knoevenagel* hetero-*Diels–Alder* and domino oxidation hetero-*Diels–Alder* reactions, in which both diene and dienophile are formed *in situ* under the same reaction conditions, and demonstrated their application in a surprising one-pot synthesis of novel 6,7-unsubstituted 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and 5-aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones **3a–3l**. Although, in this particular case, the overall yields of products **3a–3l** were low, possibly due to interference of competing reactions³⁾, we assume that the reported strategy of

²⁾ EtOH with less than 0.001% MeCHO content was used.

³⁾ Acetaldehyde, which is formed *in situ*, can compete with benzaldehyde **1a–1g** for barbituric acids **2a** and **2b** as a substrate for the *Knoevenagel* reaction. Additionally, the *Knoevenagel* product **A** can undergo *Michael* addition with a second molecule of barbituric acid.

generating both the diene and the dienophile *in situ* in two converging domino processes could open new opportunities for sequential transformations which include hetero-Diels–Alder reaction.

Experimental Part

General. All reagents were used as received from commercial sources without further purification unless otherwise indicated. Anal. TLC: Merck silica gel (60 F_{254}) plates (0.25 mm), components visualized with UV light. Column chromatography (CC): silica gel 60 (particle size 240–400 mesh; Merck). Microwave-assisted reactions were conducted in a sealed glass vessel (capacity 10 ml) on a CEM Discover microwave synthesizer (CEM Corporation, USA) with a built-in pressure measurement sensor and operator-selectable power output from 0 to 300 W. The temp. was monitored using an IR temp. sensor mounted under the reaction vessel. All experiments were performed using a high-speed stirring option. M.p.: Reichert hot stage microscope; uncorrected. IR Spectra: Perkin–Elmer 1600 FT-IR spectrometer. ^1H - and ^{13}C -NMR spectra: at 300 and 75 MHz, resp., on a Bruker AVANCE DPX300 spectrometer in (D_6)DMSO or D_2O with TMS as the internal standard at 25°. Spectra were assigned using gradient COSY, HSQC and DEPT experiments. MS: VG Analytical Autospec Q mass spectrometer. Microanalyses: Perkin–Elmer C,H,N analyzer 240 C. All reported yields are yields of purified products.

General Procedure for the Preparation of 5-Phenyl-1H-pyrano[2,3-d]pyrimidine-4(3H,5H)-ones and Their 2-Thioxo Analogs 3a–3l. Method A (Conventional Heating ⁽ⁱ⁾). A suspension of benzaldehyde **1a**–**1g** (1.00 mmol) and barbituric or 2-thiobarbituric acid (**2a** or **2b**, resp.; 1.00 mmol) in EtOH/ H_2O 1:1 (20 ml) was refluxed for 3 d, then the mixture was cooled to r.t., and the product was filtered off and washed with EtOH.

Method B (Microwave-Assisted Synthesis ⁽ⁱⁱ⁾). A suspension of benzaldehyde **1a**–**1g** (1.00 mmol), and **2a** or **2b** (1.00 mmol) in EtOH/ H_2O 1:1 (3 ml) was heated in a sealed 10-ml glass vessel in a microwave reactor for 1–2 h (Table) at 120° (power, 30 W; ramp time, 3 min). The mixture was cooled to r.t., and the product was filtered off and washed with EtOH.

1,2,3,5-Tetrahydro-5-phenyl-2-thioxo-4H-pyrano[2,3-d]pyrimidin-4-one (3a). Yield: 31 mg (24%ⁱ), 30 mg (23%ⁱⁱ). Orange crystals. M.p. 276–279°. IR (KBr): 3441, 3078, 2895, 1651, 1597, 1574, 1556, 1526, 1450, 1430, 1379, 1324, 1308, 1223, 1175, 1152, 998, 848, 787, 758, 687. ^1H -NMR (300 MHz, (D_6)DMSO): 7.49–7.51 (*m*, H–C(3'), H–C(4'), H–C(5')); 7.68–7.71 (*m*, H–C(2'), H–C(6')); 7.79 (*d*, $^3J = 15.3$, H–C(5)); 8.06 (*d*, $^3J = 12.0$, H–C(7)); 8.45 (*dd*, $^3J(5,6) = 15.3$, $^3J(6,7) = 12.0$, H–C(6)); 12.31 (*br. s*, NH); 12.34 (*br. s*, NH). ^{13}C -NMR (75 MHz, (D_6)DMSO): 116.8; 125.5; 129.7; 130.2; 132.4; 136.2; 154.6; 155.5; 161.7 (arom. C, C=O); 162.2 (arom. C, C=O); 179.4 (C=S). ESI-MS: 257 ($[M - \text{H}]^-$). HR-MS: 257.0381 ($[M - \text{H}]^-$, $\text{C}_{13}\text{H}_9\text{N}_2\text{O}_2\text{S}^-$; calc. 257.0385). Anal. calc. for $\text{C}_{13}\text{H}_9\text{N}_2\text{O}_2\text{S}$ (258.30): C 60.45, H 3.90, N 10.85; found: C 60.42, H 3.78, N 10.94.

1,5-Dihydro-5-(3-nitrophenyl)-2H-pyrano[2,3-d]pyrimidine-2,4(3H)-dione (3b). Yield: 80 mg (56%ⁱ), 50 mg (35%ⁱⁱ). Yellow crystals. M.p. 286–288°. IR (KBr): 3527, 3185, 3056, 2836, 1743, 1668, 1600, 1562, 1520, 1438, 1413, 1377, 1359, 1322, 1304, 1216, 1172, 1107, 1008, 998, 810, 794, 754, 736. ^1H -NMR (300 MHz, (D_6)DMSO): 7.73–7.82 (*m*, H–C(5), H–C(5')); 7.97 (*d*, $^3J = 11.7$, H–C(7)); 8.09 (*d*, $^3J = 7.8$, H–C(6')); 8.25–8.28 (*m*, H–C(4')); 8.40 (*s*, H–C(2')); 8.49 (*dd*, $^3J(5,6) = 15.6$, $^3J(6,7) = 11.7$, H–C(6)); 11.27 (*br. s*, NH); 11.31 (*br. s*, NH). ^{13}C -NMR (75 MHz, (D_6)DMSO): 118.3; 123.6; 125.8; 127.3; 131.7; 134.8; 137.8; 149.2; 149.8; 151.2; 153.1; 163.7 (C=O); 163.8 (C=O). ESI-MS: 286 ($[M - \text{H}]^-$). HR-MS: 286.0476 ($[M - \text{H}]^-$, $\text{C}_{13}\text{H}_8\text{N}_3\text{O}_5^-$; calc. 286.0464). Anal. calc. for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_5$ (287.23): C 54.36, H 3.16, N 14.63; found: C 54.15, H 3.11, N 14.64.

1,2,3,5-Tetrahydro-5-(3-nitrophenyl)-2-thioxo-4H-pyrano[2,3-d]pyrimidin-4-one (3c). Yield: 52 mg (34%ⁱ), 50 mg (33%ⁱⁱ). Yellow crystals. M.p. > 350°. IR (KBr): 3487, 3091, 2893, 2595, 1706, 1674, 1599, 1532, 1452, 1435, 1373, 1351, 1320, 1292, 1224, 1211, 1172, 1152, 1100, 1002, 880, 812, 785, 736, 666. ^1H -NMR (300 MHz, (D_6)DMSO): 7.78 (*t*, $^3J = 7.8$, H–C(5')); 7.88 (*d*, $^3J = 15.6$, H–C(5)); 8.02 (*d*, $^3J = 11.7$, H–C(7)); 8.14 (*d*, $^3J = 7.8$, H–C(6')); 8.28–8.31 (*m*, H–C(4')); 8.44 (*t*, $^4J = 1.8$, H–C(2')); 8.52 (*dd*, $^3J(5,6) = 15.6$, $^3J(6,7) = 11.7$, H–C(6)); 12.38 (*br. s*, NH); 12.41 (*br. s*, NH). ^{13}C -NMR (75 MHz, (D_6)DMSO): 118.4; 123.8; 126.0; 127.5; 131.7; 135.0; 137.7; 149.2; 150.7; 154.0; 161.5 (arom. C, C=O);

162.0 (arom. C, C=O); 179.5 (C=S). ESI-MS: 302 ($[M-H]^-$). HR-MS: 302.0244 ($[M-H]^-$, $C_{13}H_8N_3O_4S^-$; calc. 302.0236). Anal. calc. for $C_{13}H_8N_3O_4S$ (303.29): C 51.48, H 2.99, N 13.85; found: C 51.33, H 2.96, N 13.75.

1,5-Dihydro-5-(4-nitrophenyl)-2H-pyrano[2,3-d]pyrimidine-2,4(3H)-dione (3d). Yield: 83 mg (58%ⁱ), 66 mg (46%ⁱⁱ). Yellow crystals. M.p. > 350°. IR (KBr): 3526, 3176, 3030, 2878, 1756, 1715, 1668, 1590, 1568, 1520, 1447, 1417, 1374, 1336, 1318, 1224, 1172, 1001, 844, 794, 754, 748. ¹H-NMR (300 MHz, (D₆)DMSO): 7.79 (*d*, ³*J* = 15.6, H–C(5)); 7.90 (*d*, ³*J* = 8.7, H–C(2'), H–C(6')); 8.00 (*d*, ³*J* = 11.7, H–C(7)); 8.30 (*d*, ³*J* = 8.7, H–C(3'), H–C(5')); 8.53 (*dd*, ³*J*(5,6) = 15.6, ³*J*(6,7) = 11.7, H–C(6)); 11.29 (*br. s*, NH); 11.33 (*br. s*, NH). ¹³C-NMR (75 MHz, (D₆)DMSO): 118.8; 125.2 (C(3'), C(5')); 128.7 (C(6)); 130.2 (C(2'), C(6')); 142.3; 148.9; 149.4 (C(5)); 151.1; 152.7 (C(7)); 163.6 (C=O); 163.7 (C=O). EI-MS: 287 (*M*⁺, 100), 270 (42), 257 (8), 240 (13). HR-MS: 287.0550 (*M*⁺, $C_{13}H_9N_3O_5^+$; calc. 287.0542). Anal. calc. for $C_{13}H_9N_3O_5$ (287.23): C 54.36, H 3.16, N 14.63; found: C 54.30, H 3.06, N 14.78.

1,2,3,5-Tetrahydro-5-(4-nitrophenyl)-2-thioxo-4H-pyrano[2,3-d]pyrimidin-4-one (3e). Yield: 88 mg (58%ⁱ), 61 mg (40%ⁱⁱ). Orange crystals. M.p. > 350°. IR (KBr): 3488, 3075, 2887, 2592, 2441, 1711, 1665, 1593, 1564, 1520, 1446, 1416, 1379, 1340, 1315, 1296, 1214, 1172, 995, 841, 786, 746. ¹H-NMR (300 MHz, (D₆)DMSO): 7.85 (*d*, ³*J* = 15.3, H–C(5)), 7.92 (*d*, ³*J* = 9.0, H–C(2'), H–C(6')); 8.03 (*d*, ³*J* = 11.7, H–C(7)); 8.31 (*d*, ³*J* = 9.0, H–C(3'), H–C(5')); 8.54 (*dd*, ³*J*(5,6) = 15.3, ³*J*(6,7) = 11.7, H–C(6)); 12.38 (*br. s*, NH); 12.41 (*br. s*, NH). ¹³C-NMR (75 MHz, (D₆)DMSO): 118.8; 125.2; 128.9; 130.4; 142.2; 149.0; 150.3; 153.6; 161.5 (arom. C, C=O); 162.0 (arom. C, C=O); 179.5 (C=S). ESI-MS: 302 ($[M-H]^-$). HR-MS: 302.0243 ($[M-H]^-$, $C_{13}H_8N_3O_4S^-$; calc. 302.0236). Anal. calc. for $C_{13}H_8N_3O_4S$ (303.29): C 51.48, H 2.99, N 13.85; found: C 51.37, H 2.81, N 13.83.

3-(1,3,4,5-Tetrahydro-2,4-dioxo-2H-pyrano[2,3-d]pyrimidin-5-yl)benzonitrile (3f). Yield: 77 mg (58%ⁱ), 76 mg (57%ⁱⁱ). Yellow crystals. M.p. 308–310°. IR (KBr): 3526, 3384, 3252, 2845, 2492, 2232 (CN), 1731, 1690, 1603, 1558, 1427, 1397, 1366, 1314, 1292, 1211, 1176, 1040, 1005, 956, 837, 793, 758, 676. ¹H-NMR (300 MHz, (D₆)DMSO): 7.65–7.70 (*m*, H–C(5), H–C(5')); 7.89 (*d*, ³*J* = 7.5, H–C(4)); 7.94–7.98 (*m*, H–C(6), H–C(7)); 8.08 (*s*, H–C(2)); 8.45 (*dd*, ³*J*(5,6) = 15.6, ³*J*(6,7) = 11.7, H–C(6)); 11.26 (*br. s*, NH); 11.30 (*br. s*, NH). ¹³C-NMR (75 MHz, (D₆)DMSO): 113.3; 118.1; 119.1; 127.0; 131.3; 132.9; 133.3; 134.7; 137.3; 150.1; 151.2; 153.3; 163.6 (C=O); 163.8 (C=O). ESI-MS: 266 ($[M-H]^-$). HR-MS: 266.0570 ($[M-H]^-$, $C_{14}H_8N_3O_3^-$; calc. 266.0566). Anal. calc. for $C_{14}H_8N_3O_3$ (267.24): C 62.92, H 3.39, N 15.72; found: C 62.62, H 3.26, N 15.62.

3-(1,3,4,5-Tetrahydro-4-oxo-2-thioxo-2H-pyrano[2,3-d]pyrimidin-5-yl)benzonitrile (3g). Yield: 37 mg (26%ⁱ), 62 mg (44%ⁱⁱ). Orange crystals. M.p. 285–289°. IR (KBr): 3560, 3254, 3125, 3084, 3017, 2891, 2571, 2234 (CN), 1708, 1674, 1595, 1553, 1525, 1434, 1380, 1314, 1296, 1242, 1216, 1184, 1144, 997, 844, 817, 786, 734, 674. ¹H-NMR (300 MHz, (D₆)DMSO): 7.69 (*t*, ³*J* = 7.8, H–C(5)); 7.76 (*d*, ³*J* = 15.6, H–C(5')); 7.93 (*d*, ³*J* = 7.8, H–C(4)); 7.99–8.03 (*m*, H–C(6), H–C(7)); 8.13 (*s*, H–C(2)); 8.47 (*dd*, ³*J*(5,6) = 15.6, ³*J*(6,7) = 11.7, H–C(6)); 12.36 (*br. s*, NH); 12.39 (*br. s*, NH). ¹³C-NMR (75 MHz, (D₆)DMSO): 113.3; 118.2; 119.1; 127.3; 131.3; 133.1; 133.4; 135.0; 137.3; 151.1; 154.2; 161.5 (arom. C, C=O); 162.0 (arom. C, C=O); 179.5 (C=S). ESI-MS: 282 ($[M-H]^-$). HR-MS: 282.0336 ($[M-H]^-$, $C_{14}H_8N_3O_3S^-$; calc. 282.0337). Anal. calc. for $C_{14}H_8N_3O_3S$ (283.31): C 59.35, H 3.20, N 14.83; found: C 58.95, H 3.12, N 14.66.

4-(1,3,4,5-Tetrahydro-2,4-dioxo-2H-pyrano[2,3-d]pyrimidin-5-yl)benzonitrile (3h). Yield: 77 mg (58%ⁱ), 61 mg (46%ⁱⁱ). Yellow crystals. M.p. 316–318°. IR (KBr): 3613, 3350, 3055, 2827, 2228 (CN), 1732, 1693, 1556, 1417, 1372, 1322, 1300, 1209, 1168, 1004, 871, 846, 824, 792, 756. ¹H-NMR (300 MHz, (D₆)DMSO): 7.74 (*d*, ³*J* = 15.6, H–C(5)); 7.83 (*d*, ³*J* = 8.4, H–C(2), H–C(6)); 7.93 (*d*, ³*J* = 8.4, H–C(3), H–C(5)); 7.99 (*d*, ³*J* = 11.7, H–C(7)); 8.50 (*dd*, ³*J*(5,6) = 15.6, ³*J*(6,7) = 11.7, H–C(6)); 11.27 (*br. s*, NH); 11.31 (*br. s*, NH). ¹³C-NMR (75 MHz, (D₆)DMSO): 113.3; 118.4; 119.4; 128.0; 129.8; 133.8; 140.4; 150.1; 151.1; 153.0; 163.6 (C=O); 163.7 (C=O). ESI-MS: 266 ($[M-H]^-$). HR-MS: 266.0570 ($[M-H]^-$, $C_{14}H_8N_3O_3^-$; calc. 266.0566). Anal. calc. for $C_{14}H_8N_3O_3$ (267.24): C 62.92, H 3.39, N 15.72; found: C 62.67, H 3.30, N 15.68.

4-(1,3,4,5-Tetrahydro-4-oxo-2-thioxo-2H-pyrano[2,3-d]pyrimidin-5-yl)benzonitrile (3i). Yield: 65 mg (46%ⁱ), 85 mg (60%ⁱⁱ). Orange crystals. M.p. 310–313°. IR (KBr): 3364, 3271, 3087, 3017, 2887, 2584, 2224 (CN), 1682, 1599, 1531, 1447, 1413, 1369, 1318, 1279, 1227, 1201, 1166, 1145, 1003, 826, 801, 657. ¹H-NMR (300 MHz, (D₆)DMSO): (*d*, ³*J* = 15.6, H–C(5)); 7.84 (*d*, ³*J* = 8.4, H–C(2), H–C(6)); 7.93 (*d*,

$^3J = 8.4$, H–C(3), H–C(5)); 8.02 (d , $^3J = 11.7$, H–C(7')); 8.50 (dd , $^3J(5,6) = 15.6$, $^3J(6,7) = 11.7$, H–C(6')); 12.37 (br. s , NH); 12.40 (br. s , NH). ^{13}C -NMR (75 MHz, (D_6) DMSO): 113.5; 118.6; 119.4; 128.3; 129.9; 133.9; 140.4; 151.1; 153.8; 161.5 (arom. C, C=O); 162.0 (arom. C, C=O); 179.5 (C=S). ESI-MS: 282 ($[M - \text{H}]^-$). HR-MS: 282.0349 ($[M - \text{H}]^-$, $\text{C}_{14}\text{H}_8\text{N}_3\text{O}_2\text{S}^-$; calc. 282.0337). Anal. calc. for $\text{C}_{14}\text{H}_8\text{N}_3\text{O}_2\text{S}$ (283.31): C 59.35, H 3.20, N 14.83; found: C 59.26, H 3.11, N 14.78.

4-(1,3,4,5-Tetrahydro-2,4-dioxo-2H-pyrano[2,3-d]pyrimidin-5-yl)benzoic Acid (3j). Yield: 63 mg (44%ⁱ), 60 mg (42%ⁱⁱ). Yellow crystals. M.p. $> 350^\circ$. IR (KBr): 3550, 3284, 3054, 2847, 2652, 2519, 1731, 1694, 1607, 1598, 1568, 1549, 1506, 1440, 1415, 1383, 1319, 1295, 1238, 1214, 1175, 1113, 1052, 1013, 961, 848, 827, 790, 767. ^1H -NMR (300 MHz, (D_6) DMSO): 7.73–7.78 (m , H–C(3), H–C(5), H–C(5')); 8.00–8.04 (m , H–C(2), H–C(6), H–C(7')); 8.50 (dd , $^3J(5,6) = 15.6$, $^3J(6,7) = 11.7$, H–C(6')); 11.25 (br. s , NH); 11.29 (br. s , NH); 13.14 (br. s , COOH). ^{13}C -NMR (75 MHz, (D_6) DMSO): 117.8; 127.1; 129.4; 130.9; 133.2; 140.1; 151.2; 151.4; 153.6; 163.7 (C=O); 163.9 (C=O); 167.6 (C=O). ESI-MS: 285 ($[M - \text{H}]^-$). HR-MS: 285.0501 ($[M - \text{H}]^-$, $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_5^-$; calc. 285.0511). Anal. calc. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_5$ (286.24): C 58.74, H 3.52, N 9.79; found: C 58.46, H 3.43, N 9.66.

4-(1,3,4,5-Tetrahydro-4-oxo-2-thioxo-2H-pyrano[2,3-d]pyrimidin-5-yl)benzoic Acid (3k). Yield: 30 mg (20%ⁱ), 41 mg (27%ⁱⁱ). Orange crystals. M.p. $> 350^\circ$. IR (KBr): 3360, 3148, 3092, 2888, 2668, 2541, 1693, 1660, 1607, 1555, 1532, 1417, 1380, 1300, 1224, 1172, 1147, 1104, 998, 847, 787, 766. ^1H -NMR (300 MHz, (D_6) DMSO): 7.77–7.84 (m , H–C(3), H–C(5), H–C(5')); 8.01–8.07 (m , H–C(2), H–C(6), H–C(7')); 8.51 (dd , $^3J(5,6) = 15.6$, $^3J(6,7) = 12.0$, H–C(6')); 12.35 (br. s , NH); 12.38 (br. s , NH); 13.15 (br. s , COOH). ^{13}C -NMR (75 MHz, (D_6) DMSO): 118.0; 127.4; 129.6; 131.0; 133.4; 140.0; 152.4; 154.5; 161.6 (arom. C, C=O); 162.1 (arom. C, C=O); 167.6 (C=O); 179.5 (C=S). ESI-MS: 301 ($[M - \text{H}]^-$). HR-MS: 301.0290 ($[M - \text{H}]^-$, $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_4\text{S}^-$; calc. 301.0283). Anal. calc. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4\text{S}$ (302.31): C 55.62, H 3.33, N 9.27; found: C 55.27, H 3.35, N 8.95.

Methyl 4-(1,3,4,5-Tetrahydro-2,4-dioxo-2H-pyrano[2,3-d]pyrimidin-5-yl)benzoate (3l). Yield: 42 mg (28%ⁱ), 45 mg (30%ⁱⁱ). Yellow crystals. M.p. 296–300°. IR (KBr): 3468, 3218, 3079, 2957, 2809, 1739, 1694, 1716, 1678, 1606, 1427, 1379, 1309, 1279, 1264, 1213, 1179, 1106, 1000, 958, 827, 766, 696. ^1H -NMR (300 MHz, (D_6) DMSO): 3.88 (s , Me); 7.73–7.81 (m , H–C(3), H–C(5), H–C(5')); 8.00–8.06 (m , H–C(2), H–C(6), H–C(7')); 8.51 (dd , $^3J(5,6) = 15.6$, $^3J(6,7) = 12.0$, H–C(6')); 11.26 (br. s , NH); 11.30 (br. s , NH); 13.14 (br. s , COOH). ^{13}C -NMR: compound could not be dissolved in sufficient concentration in any known solvent. ESI-MS: 299 ($[M - \text{H}]^-$). HR-MS: 299.0670 ($[M - \text{H}]^-$, $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_5^-$; calc. 299.0668). Anal. calc. for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_5$ (300.27): C 60.00, H 4.03, N 9.33; found: C 59.79, H 3.88, N 9.34.

5-(4-Nitrobenzyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4). Yield: 42 mg (32%). Orange crystals. M.p. $> 300^\circ$ ([14]: 265–266°). IR (KBr): 3427, 3157, 3013, 2928, 2853, 1674, 1654, 1616, 1508, 1490, 1387, 1368, 1350, 1175, 1111, 860, 834, 807, 774, 700. ^1H -NMR (300 MHz, (D_6) DMSO): 3.49 (s , CH_2); 7.45 (d , $^3J = 8.7$, H–C(2), H–C(6)); 8.05 (d , $^3J = 8.7$, H–C(3), H–C(5)); 9.08 (br. s , NH); signal for CH not seen. ^{13}C -NMR (75 MHz, $\text{D}_2\text{O} + 10 \mu\text{l}$ 40% NaOD): 28.4 (CH_2); 89.0 (CH); 123.2 (arom. C); 128.2 (arom. C); 145.2 (arom. C); 151.7 (arom. C); 159.5 (C=O); 171.3 (C=O). ESI-MS: 262 ($[M - \text{H}]^-$). HR-MS: 262.0461 ($[M - \text{H}]^-$, $\text{C}_{11}\text{H}_8\text{N}_3\text{O}_5^-$; calc. 262.0464).

Preparation of 3d from 5-(4-Nitrobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione. 5-(4-Nitrobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (100 mg, 383 μmol) was heated to reflux for 3 d in EtOH/ H_2O 1:1 (20 ml), then the mixture was cooled to r.t., and the product filtered off and washed with EtOH to afford 22 mg (20%) of yellow crystals. The product was identical to the one obtained according to the General Procedure for the preparation of **3a–3l**.

Preparation of 3d from MeCHO. 4-Nitrobenzaldehyde (250 mg, 1.65 mmol) and barbituric acid (**2a**; 212 mg, 1.65 mmol) were dissolved in H_2O (40 ml) at 100° , the soln. was cooled to r.t., and acetaldehyde (280 μl , 4.96 mmol) was added. The mixture was heated at 100° for 1 h, and the product was filtered off, and washed with H_2O and EtOH to give 309 mg (65%) of yellow crystals. The product was identical to the one obtained according to the General Procedure for the preparation of **3a–3l**.

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REFERENCES

- [1] a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137; L. F. Tietze, U. Beifuss, *Angew. Chem., Int. Ed.* **1993**, *32*, 131; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; c) 'Domino Reactions in Organic Synthesis', Eds. L. F. Tietze, G. Brasche, K. M. Gericke, Wiley-VCH, Weinheim, 2006; d) L. F. Tietze, G. Kettschau, *Top. Curr. Chem.* **1997**, *189*, 1–120; e) K. C. Nicolau, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem.* **2002**, *114*, 1742; K. C. Nicolau, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem., Int. Ed.* **2002**, *41*, 1668; f) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7134; g) H. Pellissier, *Tetrahedron* **2009**, *65*, 2839; h) M. Presset, Y. Coquerel, J. Rodriguez, *Org. Lett.* **2009**, *11*, 5706; i) A. L. Lawrence, R. M. Adlington, J. E. Baldwin, V. Lee, J. A. Kershaw, A. L. Thompson, *Org. Lett.* **2010**, *12*, 1676; j) H.-B. Zhou, G.-S. Liu, Z.-J. Yao, *Org. Lett.* **2007**, *9*, 2003.
- [2] a) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem.* **2004**, *76*, 1967; b) L. F. Tietze, A. Modi, *Med. Res. Rev.* **2000**, *20*, 304; c) L. F. Tietze, N. Böhnke, S. Dietz, *Org. Lett.* **2009**, *11*, 2948; d) L. F. Tietze, C. Ott, H. Geißler, F. Haunert, *Eur. J. Org. Chem.* **2001**, 1625; e) M. Bakthadoss, G. Sivakumar, D. Kannan, *Org. Lett.* **2009**, *11*, 4466; f) G. Appendino, G. Cravotto, A. Minassi, G. Palmisano, *Eur. J. Org. Chem.* **2001**, 3711; g) L. F. Tietze, J. Bachmann, J. Wichmann, O. Burkhardt, *Synthesis* **1994**, 1185; h) M. J. Khoshkholgh, S. Balalaie, H. R. Bijanzadeh, J. H. Gross, *Synlett* **2009**, 55; i) L. F. Tietze, T. Hippe, A. Steinmetz, *Synlett* **1996**, 1043; j) J. S. Yadav, B. V. S. Reddy, V. Naveenkumar, R. S. Rao, K. Nagaiah, *Synthesis* **2004**, 1783; k) R. D. R. S. Manian, J. Jayashankaran, R. Raghunathan, *Synlett* **2007**, 874; l) D. B. Ramachary, K. Anebusely, N. S. Chowdari, C. F. Barbas III, *J. Org. Chem.* **2004**, *69*, 5838; m) B. B. Snider, Q. Lu, *J. Org. Chem.* **1996**, *61*, 2839.
- [3] a) D. Prajapati, M. Gohain, *Beilstein J. Org. Chem.* **2006**, *2*, DOI: 10.1186/1860-5397-2-11; b) M. J. Khoshkholgh, S. Balalaie, H. R. Bijanzadeh, F. Rominger, J. H. Gross, *Tetrahedron Lett.* **2008**, *49*, 6965; c) M. J. Khoshkholgh, S. Balalaie, R. Gleiter, F. Rominger, *Tetrahedron* **2008**, *64*, 10924; d) A. Pałasz, *Org. Biomol. Chem.* **2005**, *3*, 3207.
- [4] G. Kaupp, M. R. Naimi-Jamal, J. Schmeyer, *Tetrahedron* **2003**, *59*, 3753; M. L. Deb, P. J. Bhuyan, *Tetrahedron Lett.* **2005**, *46*, 6453; J. C. Ruble, A. R. Hurd, T. A. Johnson, D. A. Sherry, M. R. Barbachyn, P. L. Toogood, G. L. Bundy, D. R. Graber, G. M. Kamilar, *J. Am. Chem. Soc.* **2009**, *131*, 3991; Y. Hu, Z.-C. Chen, Z.-G. Le, Q.-G. Zheng, *Synth. Commun.* **2004**, *34*, 4521.
- [5] A. H. Shamroukh, M. E. A. Zaki, E. M. H. Morsy, F. M. Abdel-Motti, F. M. E. Abdel-Megeid, *Arch. Pharm.* **2007**, *340*, 236.
- [6] A. H. Bedair, H. A. Emam, N. A. El-Hady, K. A. R. Ahmed, A. M. El-Agrody, *Farmaco* **2001**, *56*, 965.
- [7] V. K. Ahluwalia, R. Batla, A. Khurana, R. Kumar, *Indian J. Chem. B* **1990**, *29*, 1141.
- [8] I. O. Zhuravel, S. A. Grashenkova, L. V. Yakovleva, O. V. Borisov, S. M. Kovalenko, V. P. Chernikh, *Zh. Org. Khim.* **2006**, *4*, 25.
- [9] J. W. G. Meissner, A. C. van der Laan, U. K. Pandit, *Tetrahedron Lett.* **1994**, *35*, 2757; B. S. Jursic, D. M. Neumann, *Tetrahedron Lett.* **2001**, *42*, 4103; B. S. Jursic, E. D. Stevens, *Tetrahedron Lett.* **2003**, *44*, 2203.
- [10] K. Tanaka, X. Chen, T. Kimura, F. Yoneda, *Chem. Pharm. Bull.* **1986**, *34*, 3945; K. Tanaka, X. Chen, T. Kimura, F. Yoneda, *Chem. Pharm. Bull.* **1988**, *36*, 60.
- [11] K. Tanaka, X. Chen, T. Kimura, F. Yoneda, *Tetrahedron Lett.* **1987**, *28*, 4173; K. Tanaka, X. Chen, F. Yoneda, *Tetrahedron* **1988**, *44*, 3241.
- [12] T. Tomašić, N. Zidar, V. Rupnik, A. Kovač, D. Blanot, S. Gobec, D. Kikelj, L. Peterlin Mašič, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 153.
- [13] T. Tomašić, N. Zidar, A. Kovač, S. Turk, M. Simčič, D. Blanot, M. Müller-Premru, M. Filipič, S. Golič Grdadolnik, A. Zega, M. Anderluh, S. Gobec, D. Kikelj, L. Peterlin Mašič, *ChemMedChem* **2010**, *5*, 286.
- [14] J. V. Tate, W. N. Tinnerman II, V. Jurevics, H. Jeskey, E. R. Biehl, *J. Heterocycl. Chem.* **1986**, *23*, 9.

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