A Green Approach to the Synthesis of Fused Uracils: Pyrano[2,3-*d*]pyrimidines. 'On-Water' One-Pot Synthesis by Domino Knoevenagel/Diels–Alder Reactions

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Abstract: 'On-water' Knoevenagel condensations of 2-thiobarbituric acid and *N*,*N*-dimethylbarbituric acid with aromatic and heteroaromatic aldehydes were carried out without a catalyst and at room temperature. Condensations in aqueous suspensions occurred rapidly, giving excellent yields. Solvent-free hetero-Diels–Alder reactions of 5-arylidene derivatives of barbituric acids with ethyl vinyl ether were investigated at room temperature and pyrano[2,3-*d*]pyrimidines of potential pharmacological activity were obtained in excellent yields. Three-component one-pot syntheses of annulated uracils were performed in aqueous suspensions. Reactions of barbituric acids, aldehydes, and ethyl vinyl ether were carried out at ambient temperature, whereas the one-pot synthesis with barbituric acids, aldehydes, and styrene or *N*-vinyl-2-oxazolidinone required the heating of aqueous suspensions at 60 °C. 'On-water' cycloadditions were characterized by high diastereoselectivity in contrast to reactions carried out in homogeneous organic media (dichloromethane, toluene). They allowed the *cis* adducts to be obtained preferentially or exclusively. The presented green methods avoid the use of catalysts, the heating of reaction mixtures for long times at high temperatures, and the use of organic solvents, and make the synthesis of a variety of pyrano[2,3-*d*]pyrimidines chemically efficient. The results reveal water as the medium of choice for the examined cycloadditions.

Key words: Diels–Alder reactions, drugs, green chemistry, pyrano[2,3-*d*]pyrimidines, solvent effects

Water is the solvent of choice for nature to carry out syntheses of complex organic molecules. Water is a clean, inexpensive, environmentally friendly reaction medium. Therefore the choice of water as solvent for organic reactions in the laboratory is obvious. However, water as a solvent was ruled out from organic reactions during the preceding decades. The situation changed in 1980 by the pioneering work of Breslow and Rideout, who demonstrated that Diels–Alder reactions of water-soluble reagents would be greatly accelerated in aqueous solution.[1a] In 2005, Sharpless and co-workers demonstrated that the Diels–Alder reaction of the water-insoluble reactants showed substantial rate acceleration in aqueous suspension over homogeneous solution.[1b] Hydrophobic interactions of reagents with water are invoked for the observed effects.

Barbituric acids and their derivatives are reported to have a wide range of pharmacological activities. For example, 5,5-disubstituted derivatives, known as barbiturates, are a family of valuable drugs that depress nerve activity.[2] 5-Arylidene derivatives of barbituric acids are bioactive compounds[3] and are also important intermediates in the preparation of other pharmaceuticals, for example annulated uracils. Uracil and its fused derivatives, such as pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines, pyrazo[3,4-*d*]pyrimidines, or pyrimido[4,5-*d*]pyrimidines, are reported to have a wide range of biological activities such as antiallergic,[4] antihypertensive,[5] cardiotonic,[6] bronchiodilator,[7] antibronchitic,[8] or antitumor[9] activity.

The preparation of the above-mentioned compounds containing a uracil ring poses significant synthetic challenges. The synthesis of annulated uracils is well described in the literature,[10] but the synthetic methods usually require drastic conditions, long reaction times, and complex synthetic pathways and the yields are poor. There have been novel approaches to the synthesis of annulated uracils of biological importance recently. These new synthetic methods rely on a multicomponent reaction in the solid state,[11] a stereoselective intramolecular hetero-Diels–Alder reaction (HDA),[12] an intermolecular [4+2]-cycloaddition reaction,[13] or a photo-induced oxidative cyclization.[14] The HDA is an excellent method for the synthesis of fused uracils, because this reaction is a simple and efficient tool for the construction of six-membered heterocyclic systems. As active heterodienes in Diels–Alder reactions, 5-arylidene derivatives of barbituric acid are used. The Knoevenagel condensation of various aromatic and heteroaromatic aldehydes with active methylene compounds such as barbituric acids, Meldrum's acid, dimedone, malononitrile, or ethyl cyanoacetate has been widely used in the synthesis of arylidene derivatives. The reactions with aromatic aldehydes are usually catalyzed by bases[15] such as amines, ammonia, or sodium ethoxide. Acids such as acetic acid, hydrochloric acid, or sulfuric acid can also be used as catalysts.[16]

As a continuation of the investigations of organic reactions performed in aqueous medium, a green method for the synthesis of the fused uracils 2-thioxopyrano[2,3-*d*]pyrimidin-4-ones and pyrano[2,3-*d*]pyrimidin-2,4-diones by uncatalyzed Knoevenagel condensation 'on water' at room temperature and a solvent-free hetero-Diels–Alder cycloaddition at room temperature is reported.

5-Arylidene-2-thiobarbituric acids **3a**–**g** and 5-arylidene-*N*,*N*-dimethylbarbituric acids **3h**–**m**, as potential heterodienes in Diels–Alder reactions, were synthesized by

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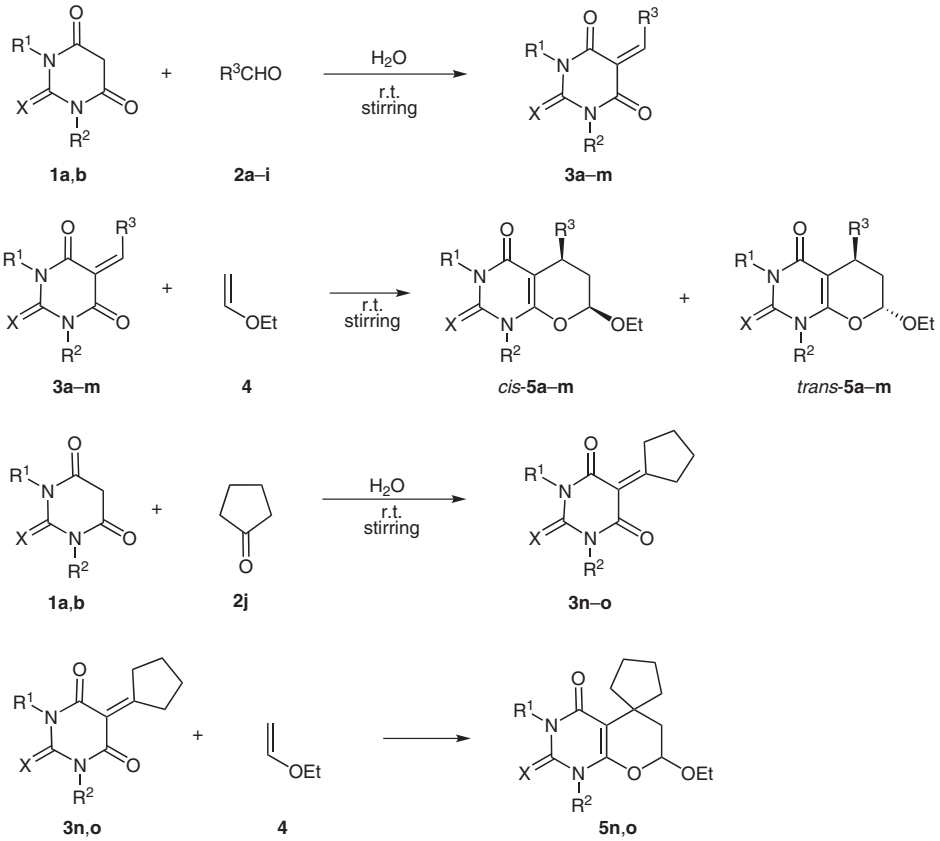
modification of the procedure described in literature (Scheme 1, Table 1).[17] Condensations of 2-thiobarbituric acid **1a** or *N*,*N*-dimethylbarbituric acid **1b** with appropriate aromatic or heteroaromatic aldehydes **2a–i** were carried out in water without catalyst at room temperature. It is worth noting that Bhuyan et al.[17] described this method for barbituric acid and *N*,*N*-dimethylbarbituric acid, soluble in water at room temperature. In the present work this method was for the first time used for water-insoluble 2-thiobarbituric acid. It is reported in the literature[3] that 5-arylidene derivatives of 2-thiobarbituric acid were obtained by an uncatalyzed Knoevenagel condensation in aqueous medium, but the solution was heated at 80 °C for several hours. In the present study it was found that the heating of the reaction mixture is not necessary and that it is also not necessary to dissolve the 2-thiobarbituric acid in water by heating before the addition of the aldehyde. The examined reactions are examples of 'on-water' reactions, in which insoluble reactants are stirred in aqueous suspension. All the reactions occurred rapidly and were completed in just an hour, giving excellent yields of 88–98% of Knoevenagel products **3a–m** (Tables 1 and 2).

The cycloaddition reactions of 5-arylidenebarbituric acids **3a–m** with a tenfold excess of ethyl vinyl ether (**4**) were performed in the absence of solvent at room temperature for one to five hours, and the uracils **5a–m** were obtained in excellent 88–96% yields (Scheme 1, Tables 1 and 2). Previously, I described reactions of 5-arylidene derivatives of *N*,*N*-dimethylbarbituric acids **3h–m** with enol ether **4** at room temperature, but dichloromethane was used as solvent.[18] While reaction mixtures **3a–m** with **4** without solvent were stirred, solid compounds **3a–m** did not dissolve in a tenfold excess of **4**, but a change in the color of the precipitate from the yellow of dienes **3a–m** to the colorless cycloadducts **5a–m** was observed.

Next, the 'on-water' Knoevenagel condensation procedures, used for aldehydes **2a–i**, were applied to cyclic ketones such as cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone. There are no reports in the literature describing such green procedures for ketones, because they have too low reactivity in the condensations with CH acids. Only cyclopentanone gave cyclopentylidene derivatives **3n**,**o** in excellent 93 and 95% yield, respectively, without further purification (Scheme 1, Tables 1 and 2, entries 14 and 15). The Diels–Alder reactions of the Knoevenagel products **3n**,**o** with a tenfold excess of **4** needed heating in ethyl acetate at 77 °C for four hours, and the spirouracils **5n**,**o** were synthesized in good yields (88 and 91%, respectively; Table 2, entries 14 and 15).

The progress of all the reactions was monitored by TLC. The ratios of the *cis* and *trans* diastereoisomers of the pyrano[2,3-*d*]pyrimidines **5a–m** were determined on the basis of the ^{1}H NMR spectra of the crude products, by analysis of the signal of proton H-7. All diastereoisomers of compounds **5a–m** were separated by column chromatography by using ethyl acetate as eluent. Cycloadducts **5a–g** prepared from 2-thiobarbituric acid are new com-



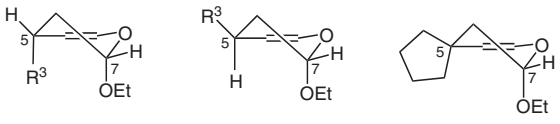
Scheme 1

Table 1 Synthesis of Pyrano[2,3-*d*]pyrimidines **5a–o** by Solvent-Free HDA Reactions of 5-Arylidene-2-thiobarbituric Acids **3a–g**, 5-Arylidene-*N*,*N*-dimethylbarbituric Acids **3h–m**, or Barbituric Acids **3n**,**o** with Enol Ether **4**

Entry	**1**	R^1	R^2	X	**2**	R^3	**3**	**5**
1	**1a**	H	H	S	**2a**	C_6H_5	**3a**	**5a**
2	**1a**	H	H	S	**2b**	4-$MeOC_6H_4$	**3b**	**5b**
3	**1a**	H	H	S	**2c**	4-NCC_6H_4	**3c**	**5c**
4	**1a**	H	H	S	**2d**	4-ClC_6H_4	**3d**	**5d**
5	**1a**	H	H	S	**2e**	4-BrC_6H_4	**3e**	**5e**
6	**1a**	H	H	S	**2f**	2-thienyl	**3f**	**5f**
7	**1a**	H	H	S	**2g**	2-furyl	**3g**	**5g**
8	**1b**	Me	Me	O	**2a**	C_6H_5	**3h**	**5h**
9	**1b**	Me	Me	O	**2b**	4-$MeOC_6H_4$	**3i**	**5i**
10	**1b**	Me	Me	O	**2h**	4-$O_2NC_6H_4$	**3j**	**5j**
11	**1b**	Me	Me	O	**2f**	2-thienyl	**3k**	**5k**
12	**1b**	Me	Me	O	**2g**	2-furyl	**3l**	**5l**
13	**1b**	Me	Me	O	**2i**	4-pyridyl	**3m**	**5m**
14	**1a**	H	H	S	**2j**	–[a]	**3n**	**5n**
15	**1b**	Me	Me	O	**2j**	–[a]	**3o**	**5o**

[a] See Scheme 1 for the structures of **3n**,**o** and **5n**,**o**.

pounds, not yet described in the literature. The relative *cis* and *trans* configurations of the C-5 and C-7 substituents were assigned on the basis of ^{1}H NMR spectra. They were deduced from the chemical shift values and coupling constants of the protons attached to C-5 and C-7 of the dihydropyran ring that exists in a half-chair conformation (Figure 1).[19]



major *cis*-**5a–g** minor *trans*-**5a–g** **5n**,**o**

Figure 1 Preferred *cis*/*trans* configurations and conformations of cycloadducts **5a–g** and **5n**,**o**, determined on the basis of ^{1}H NMR analysis

In the ^{1}H NMR spectra of the major diastereoisomers *cis*-**5a–g**, the signal of H-5 appeared as a doublet of doublets at δ = 3.79–4.14, with coupling constants ^3J = 6.9–7.2 and 3.6–5.1 Hz due to coupling with two protons at C-6 (Figure 1, Table 3). Thus, H-5 occupies the *pseudo-equatorial* position, and the aromatic group adopts the *pseudo-axial* orientation (Figure 1).The ^{1}H NMR spectra of *cis*-**5a–g** reveal the signals of proton H-7 as a doublet of doublets at δ = 5.46–5.52 with two small coupling constants (^3J = 3.3–4.8 and 2.4–3.0 Hz). Thus, H-7 is in the *equatorial* position and the alkoxy group occupies the *axial* position (Figure 1).

Table 2 Synthesis of Pyrano[2,3-*d*]pyrimidines **5a–o** by Solvent-Free HDA Reactions of **3a–o** with **4**

Entry	**3**	Yield (%) of **3**	**5**	Reaction time (h)	Yield (%)[a] of **5**	Ratio *cis*/*trans*[a]
1	**3a**	93	**5a**	1	88	2.1:1
2	**3b**	90	**5b**	1	96	2.3:1
3	**3c**	91	**5c**	2	92	1:1
4	**3d**	89	**5d**	3	89	3.4:1
5	**3e**	88	**5e**	3	92	2.8:1
6	**3f**	91	**5f**	5	90	1:1.5
7	**3g**	95	**5g**	5	89	1:1
8	**3h**	91	**5h**	1	94	1.8:1
9	**3i**	98	**5i**	1	95	2.5:1
10	**3j**	95	**5j**	2	95	1.2:1
11	**3k**	92	**5k**	5	91	2.6:1
12	**3l**	91	**5l**	5	92	1.9:1
13	**3m**	93	**5m**	5	90	1.8:1
14	**3n**	93	**5n**	4[b]	88	–
15	**3o**	95	**5o**	4[b]	91	–

[a] Ratio based on ^{1}H NMR (300 MHz) spectra of crude products.
[b] Reaction mixture was heated in EtOAc at 77 °C.

For the minor diastereoisomers *trans*-**5a–g**, the protons attached to C-5 give rise to a doublet of doublets with coupling constants ^3J = 5.1–7.2 and 4.2–6.6 Hz at δ = 3.71–4.16 (Table 3). Thus, H-5 is *pseudo-axial* and the aryl moiety occupies the *pseudo-equatorial* position (Figure 1). The proton H-7 of *trans*-**5a–g** resonates at δ = 5.16–5.29 as a doublet of doublets with two coupling constants ^3J = 5.7–7.5 and 2.1–5.4 Hz. This suggests that for *trans*-**5a–g** the conformation with an *axial* alkoxy group is preferred due to stabilization by the anomeric effect. Cycloadducts *cis*-**5a–g** were the major products. The preferred formation of the *cis* diastereoisomers (see Table 2) results from the *endo* transition state interaction, which is energetically more favorable than the *exo* transition state. Thus, *cis* products arise from a kinetically controlled process.[20] The stereochemical structure of *cis*/*trans* cycloadducts **5h–m** was described in previous work.[18] The orientation of the ethoxy substituent at C-7′ was assigned on the basis of ^{1}H NMR spectra. It was deduced from the chemical shift values and the coupling constants of the proton attached to C-7′ of the dihydropyran ring that exists in a half-chair conformation.[19] In the ^{1}H NMR spectra of spiropyrans **5n**,**o**, the signal of H-7′ appears as a doublet of doublets at δ = 5.08–5.29 with coupling constants ^3J = 2.1 and 6.9–8.1 Hz due to coupling with two protons at C-6′. Thus, H-7′ is in the *equa-*

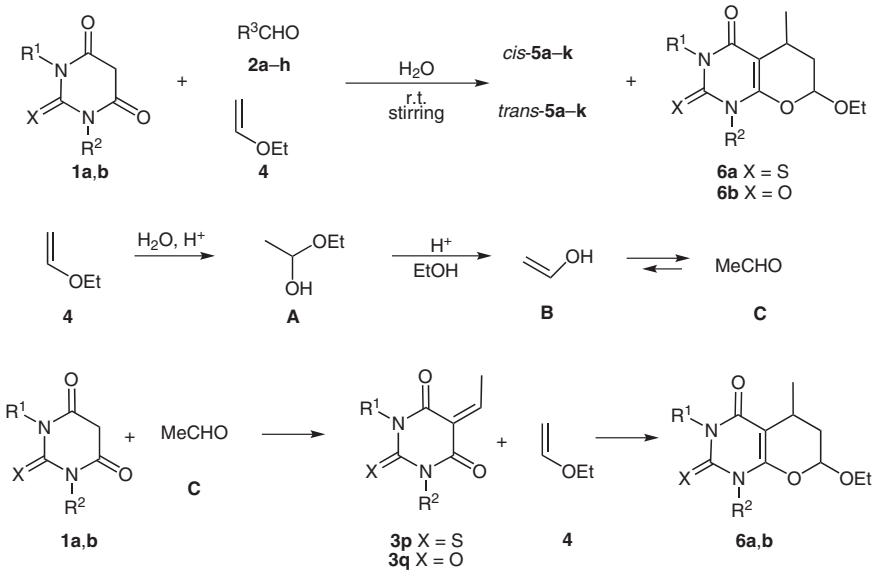
Table 3 Signals of H-5 and H-7 in the ^{1}H NMR Spectra of 2-Thioxopyrano[2,3-*d*]pyrimidin-4-ones **5a–g**

cis-**5**	δ (dd, H-5) (ppm) $J_{6ax,5}/J_{6eq,5}$ (Hz)	δ (dd, H-7) (ppm) $J_{6ax,7}/J_{6eq,7}$ (Hz)	*trans*-**5**	δ (dd, H-5) (ppm) $J_{6ax,5}/J_{6eq,5}$ (Hz)	δ (dd, H-7) (ppm) $J_{6ax,7}/J_{6eq,7}$ (Hz)
cis-**5a**	3.86 7.2/5.1	5.47 4.5/2.7	*trans*-**5a**	3.87 6.3/5.4	5.19 7.5/2.4
cis-**5b**	3.79 7.2/4.8	5.46 4.8/2.4	*trans*-**5b**	3.83 6.6/4.8	5.16 7.5/2.4
cis-**5c**	3.94 7.2/3.9	5.50 3.3/3.0	*trans*-**5c**	3.92 6.6/6.6	5.29 6.3/2.4
cis-**5d**	3.85 6.9/4.2	5.48 3.6/2.7	*trans*-**5d**	3.71 7.2/5.7	5.23 6.6/2.4
cis-**5e**	3.84 7.2/4.5	5.48 3.9/2.7	*trans*-**5e**	3.84 6.6/6.6	5.23 6.9/2.1
cis-**5f**	4.14 6.9/3.6	5.52 3.3/3.0	*trans*-**5f**	4.16 5.1/4.2	5.25 5.7/5.4
cis-**5g**	3.94 6.9/3.9	5.51 3.0/2.7	*trans*-**5g**	3.85 6.6/6.3	5.23 7.5/2.4

torial position and the alkoxy group occupies the *axial* position (Figure 1).

It is well-known that a Knoevenagel condensation followed by a hetero-Diels–Alder reaction, realized as a one-pot synthesis, can be used in dihydropyran preparation.[21] Therefore, in the next step of these studies, three-component one-pot synthesis of uracils **5a–k** by domino Knoevenagel/Diels–Alder reactions was investigated in aqueous medium. The Knoevenagel product was formed in situ in aqueous suspensions and the next hetero-Diels–Alder reaction proceeded smoothly in biphasic conditions. The experimental procedure was simple: equimolar amounts of barbituric acids **1a**,**b** and aromatic or heteroaromatic aldehydes **2a–h** were mixed with a tenfold excess of enol ether **4** in water at room temperature for one to three hours, and the pyrano[2,3-*d*]pyrimidines **5a–k** and, unexpectedly, products **6a**,**b** were obtained in 88–96% yields (Scheme 2, Tables 4 and 5). While the reaction mixtures of **1a**,**b**, **2a–h**, and **4** were stirring as aqueous suspensions, a change of the precipitate color from yellow to colorless was observed; this is characteristic for cycloadducts **5a–k**.

The progress of the reactions was monitored by TLC. The molar ratios of the *cis*-**5**/*trans*-**5**/**6** derivatives of pyrano[2,3-*d*]pyrimidines were determined on the basis of the ^{1}H NMR spectra of the crude products and also on the basis of the mass of the products obtained after column chromatography. The major products in the 'on-water' one-pot synthesis were compounds *cis*-**5a–k**. Formation of the unexpected 5-methyl-substituted derivatives of pyrano[2,3-*d*]pyrimidines **6a**,**b** can be explained as shown in Scheme 2. In the first step, the addition of water to alkene



Scheme 2

Table 4 Synthesis of Pyrano[2,3-*d*]pyrimidines **5a**–**k** and **6a**,**b** by 'On-Water' Three-Component One-Pot Reactions amongst **1a**,**b**, **2a**–**h**, and **4**

Entry	**1**	R^1	R^2	X	**2**	R^3	**5**	**6**
1	**1a**	H	H	S	**2a**	C_6H_5	**5a**	**6a**
2	**1a**	H	H	S	**2b**	4-$MeOC_6H_4$	**5b**	**6a**
3	**1a**	H	H	S	**2c**	4-NCC_6H_4	**5c**	**6a**
4	**1a**	H	H	S	**2d**	4-ClC_6H_4	**5d**	**6a**
5	**1a**	H	H	S	**2e**	4-BrC_6H_4	**5e**	**6a**
6	**1a**	H	H	S	**2f**	2-thienyl	**5f**	**6a**
7	**1b**	Me	Me	O	**2a**	C_6H_5	**5h**	**6b**
8	**1b**	Me	Me	O	**2b**	4-$MeOC_6H_4$	**5i**	**6b**
9	**1b**	Me	Me	O	**2h**	4-$O_2NC_6H_4$	**5j**	**6b**
10	**1b**	Me	Me	O	**2f**	2-thienyl	**5k**	**6b**

Table 5 Synthesis of Pyrano[2,3-*d*]pyrimidines **5a**–**k** and **6a**,**b** by 'On-Water' Three-Component One-Pot Reactions

Entry	**5**	**6**	Time (h)	Yield (%)[a]	Ratio (**6** + *cis*-**5**)/ *trans*-**5**[b]	Ratio **6**/*cis*-**5**/ *trans*-**5**[d]
1	**5a**	**6a**	1	88	9.2:1[c]	2.5:6.4:1
2	**5b**	**6a**	1	96	10.0:1	1.8:8.5:1
3	**5c**	**6a**	2	92	7.8:1	1.6:6.0:1
4	**5d**	**6a**	2	89	8.1:1	1.7:6.5:1
5	**5e**	**6a**	2	92	7.2:1	2.0:5.2:1
6	**5f**	**6a**	3	90	7:1	0.5:6.3:1
7	**5h**	**6b**	1	94	1.5:4.3:1	1.3:4.1:1
8	**5i**	**6b**	1	95	1.8:6.6:1	1.5:6.6:1
9	**5j**	**6b**	2	95	1.5:5.5:1	1.4:5.3:1
10	**5k**	**6b**	3	91	0.5:5.6:1	0.6:5.3:1

[a] Isolated yields after column chromatography.
[b] Ratio based on analysis of signal of proton H-7 of **6**, *cis*-**5**, and *trans*-**5** in ^{1}H NMR (300 MHz) spectra of crude products.
[c] Overlap of δ = 5.43 (dd) and 5.47 (dd) of H-7 for **6a** with δ = 5.46–5.52 of H-7 for *cis*-**5a**–**f**.
[d] Molar ratio based on mass of products obtained after column chromatography.

4 catalyzed by barbituric acid provides hemiacetal **A**, which undergoes ethanol elimination to produce enol tautomer **B** or keto tautomer of acetaldehyde **C**. Next, the in situ generated aldehyde **C** undergoes Knoevenagel condensation with barbituric acids **1a**,**b** to furnish intermediate condensation product **3p**,**q**. In the final step, Diels–Alder reaction of intermediate **3p**,**q** with ethyl vinyl ether **4** resulted in the unexpected products **6a**,**b**. Compounds **6a**,**b** are new and have not been described in the literature yet. It was determined on the basis of the ^{1}H NMR spectra of the crude products that only one of the two diastereoisomers *cis*/*trans* **6a**,**b** was created. Compounds **6a**,**b** were observed as one spot on TLC plates when ethyl acetate or ethyl acetate–petroleum ether (5:1) were used as eluent. It is impossible to assign the relative *cis* or *trans* configuration of the C-5 and C-7 substituents in cycloadducts **6a**,**b** unambiguously on the basis of the ^{1}H NMR spectra.

Three-component one-pot syntheses of pyrano[2,3-*d*]pyrimidines performed in aqueous suspension were faster than those executed in dichloromethane[18] or under solventless conditions. The 'on-water' one-pot synthesis (OPS) gave the highest yields and the *endo*/*exo* selectivity was significantly improved (Table 6).

Table 6 Comparison of Reaction Times, Yields, and Ratios of *cis*-**5**/*trans*-**5** for the Synthesis of Pyrano[2,3-*d*]pyrimidines **5b**, **5f**, **5i**, and **5k** under Different Reaction Conditions

5	Medium	Reaction time (h)	Yield (%)	Ratio *cis*-**5**/ *trans*-**5**
5b	no solvent	1	96	2.3:1
5b	OPS[a] 'on-water'	1	96	8.5:1:1.8[c]
5b	CH_2Cl_2[b]	3	94	2.2:1
5b	OPS in CH_2Cl_2[b]	4	92	2.4:1
5f	no solvent	5	90	1.0:1.5
5f	OPS 'on-water'	3	90	6.3:1:0.5[c]
5f	CH_2Cl_2[b]	8	84	1.0:1.1
5f	OPS in CH_2Cl_2[b]	8	87	1.0:1.0
5i	no solvent	1	95	2.5:1
5i	OPS 'on-water'	1	95	6.6:1:1.5[d]
5i	CH_2Cl_2[b]	2	94	2.6:1
5i	OPS in CH_2Cl_2[b]	3	95	2.6:1
5k	no solvent	5	91	2.6:1
5k	OPS 'on-water'	3	91	5.3:1:0.6[d]
5k	CH_2Cl_2[b]	5	84	1.25:1
5k	OPS in CH_2Cl_2[b]	7	87	2.6:1

[a] OPS = one-pot synthesis.
[b] Diels–Alder reactions of **3g**–**m** with **4** at r.t. in CH_2Cl_2 and OPS of uracils **5g**,**m** in CH_2Cl_2 are described in a previous paper.[18] Syntheses of **5b** and **5f** in CH_2Cl_2 were carried out according to the procedure reported in ref. 18.
[c] Ratio *cis*-**5**/*trans*-**5**/**6a**.
[d] Ratio *cis*-**5**/*trans*-**5**/**6b**.

Next, 'on-water' one-pot syntheses of uracils **8a**–**h** by reaction of barbituric acids **1a** or **1b**, aldehydes **2a** or **2h**, and styrene **7a** or *N*-vinyl-2-oxazolidinone **7b** were examined (Scheme 3, Table 7). Equimolar amounts of compounds **1**, **2**, and **7** were mixed in water at 60 °C for one to three hours, and the pyrano[2,3-*d*]pyrimidines **8a**–**h** were obtained in 89–95% yields (Table 8). The only products

of the reactions were *cis*-**8a–h** diastereoisomers. Cycloadducts **8a–d** prepared from 2-thiobarbituric acid are new compounds and have not yet been described in the literature. The relative *cis* configuration of the C-5 and C-7 substituents in compounds **8a–h** was assigned on the basis of analysis of the signals of the protons attached to C-5 and C-7 of the dihydropyran ring in the ^{1}H NMR spectra (Figure 2, Table 9). In previous papers,[22,23] it was shown that reactions 5-arylidene-*N*,*N*-dimethylbarbituric acids with styrenes or *N*-vinyl-2-oxazolidinone required refluxing in toluene for 24–36 hours for styrenes[22] and 3–5 hours for *N*-vinyl-2-oxazolidinone.[23] The reactions performed 'on water' in heterogeneous phase were faster (1–3 h) than those executed in refluxing toluene solution. The 'on-water' reactions were characterized by very high *endo*/*exo* diastereoselectivity in contrast to reactions in boiling toluene for which a *cis*/*trans* diastereoselectivity of 1:1 was observed.

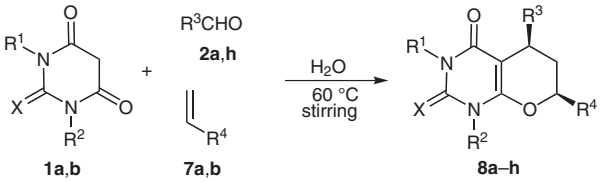
Table 7 Synthesis of Pyrano[2,3-*d*]pyrimidines **8a–h** by 'On-Water' Three-Component One-Pot Reactions amongst **1a**,**b**, **2a**,**h**, and **7a**,**b**

Entry	1	2	R^3	7	R^4	8
1	**1a**	**2a**	C_6H_5	**7a**	4-$MeOC_6H_4$	**8a**
2	**1a**	**2h**	4-$O_2NC_6H_4$	**7a**	4-$MeOC_6H_4$	**8b**
3	**1a**	**2a**	C_6H_5	**7b**	2-oxooxazolidin-3-yl	**8c**
4	**1a**	**2h**	4-$O_2NC_6H_4$	**7b**	2-oxooxazolidin-3-yl	**8d**
5	**1b**	**2a**	C_6H_5	**7a**	4-$MeOC_6H_4$	**8e**
6	**1b**	**2h**	4-$O_2NC_6H_4$	**7a**	4-$MeOC_6H_4$	**8f**
7	**1b**	**2a**	C_6H_5	**7b**	2-oxooxazolidin-3-yl	**8g**
8	**1b**	**2h**	4-$O_2NC_6H_4$	**7b**	2-oxooxazolidin-3-yl	**8h**

Table 8 Synthesis of Pyrano[2,3-*d*]pyrimidines **8a–h** by 'On-Water' Three-Component One-Pot Reactions amongst **1a**,**b**, **2a**,**h**, and **7a**,**b**

Entry	1	2	7	8	Reaction time (h)	Yield (%)[a]	Ratio *cis*-**8**/*trans*-**8**[b]
1	**1a**	**2a**	**7a**	**8a**	3	89	>100:1
2	**1a**	**2h**	**7a**	**8b**	2	94	>100:1
3	**1a**	**2a**	**7b**	**8c**	2	91	>100:1
4	**1a**	**2h**	**7b**	**8d**	1	92	>100:1
5	**1b**	**2a**	**7a**	**8e**	2	91	>100:1
6	**1b**	**2h**	**7a**	**8f**	1	93	>100:1
7	**1b**	**2a**	**7b**	**8g**	2	90	>100:1
8	**1b**	**2h**	**7b**	**8h**	1	95	>100:1

[a] Isolated yields after column chromatography.
[b] Ratio based on analysis of signal of proton H-7 of *cis*-**8** and *trans*-**8** in ^{1}H NMR (300 MHz) spectra of crude products.



Scheme 3

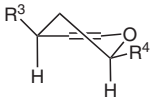


Figure 2 Preferred *cis* configuration of **8a–h**

In conclusion, very simple and highly efficient green methods for the synthesis of fused uracils, namely pyrano[2,3-*d*]pyrimidines of potential pharmacological activity, were described. The Knoevenagel condensations of aromatic and heteroaromatic aldehydes **2a–g** with 2-thiobarbituric acid **1a** were carried out in aqueous suspensions as 'on-water' reactions without catalyst and at room temperature. Condensations occurred rapidly and were completed in only an hour giving good yields (88–95%) of Knoevenagel products **3a–g**. Solvent-free hetero-Diels–Alder reactions of 5-arylidene derivatives of barbituric acids **1a**,**b** with ethyl vinyl ether **4** were carried out at room temperature. Cycloadducts **5a–m** were obtained in excellent yields (88–96%). The same 'on-water' procedures for Knoevenagel condensation at room temperature, without catalyst, were used for cyclopentanone. Cyclopentylidene derivatives **3n**,**o** were obtained in excellent

Table 9 Signals of Protons H-5 and H-7 in the ^{1}H NMR Spectra of 2-Thioxopyrano[2,3-*d*]pyrimidin-4-ones *cis*-**8a–h**

cis-**8**	δ (dd, H-5) (ppm) $J_{6ax,5}/J_{6eq,5}$ (Hz)	δ (dd, H-7) (ppm) $J_{6ax,7}/J_{6eq,7}$ (Hz)	*cis*-**8**	δ (dd, H-5) (ppm) $J_{6ax,5}/J_{6eq,5}$ (Hz)	δ (dd, H-7) (ppm) $J_{6ax,7}/J_{6eq,7}$ (Hz)
cis-**8a**	3.96 11.3/6.6	5.49 11.3/1.8	*cis*-**8e**	4.18 11.3/6.7	5. 21 11.5/2.0
cis-**8b**	4.10 11.1/6.5	5.51 11.3/2.0	*cis*-**8f**	4.22 11.2/6.8	5.23 11.8/1.8
cis-**8c**	4.05 11.0/6.3	5.91 11.1/1.8	*cis*-**8g**	4.29 11.2/6.5	5.93 11.0/6.7
cis-**8d**	4.09 11.3/6.5	5.96 11.0 / 2.1	*cis*-**8h**	4.31 11.3/6.6	5. 95 11.3/6.5

yields (93–95%). Diels–Alder reactions of compounds **3n**,**o** with vinyl ether **4** needed heating in ethyl acetate and the spirouracils **5n**,**o** were synthesized in good yields (88–91%). Three-component one-pot syntheses of annulated uracils by domino Knoevenagel/Diels–Alder reactions of barbituric acids **1a**,**b**, aldehydes **2a**–**h**, and ethyl vinyl ether **4** were performed in aqueous suspension at ambient temperature, whereas one-pot synthesis from **1a**,**b**, **2a**,**h**, and styrene **7a** or *N*-vinyl-2-oxazolidinone **7b** required heating of aqueous suspensions at 60 °C. They furnished the Diels–Alder products **5a**–**k** in 88–96% and **8a**–**h** in 89–95% yields after one to three hours. Formation of cycloadducts **5a**–**k** was accompanied by the unexpected formation of 5-methyl-substituted derivatives of pyrano[2,3-*d*]pyrimidines **6a**,**b**. The *endo-cis* adducts **5** were preferentially or exclusively produced. The results suggest that the presented green methods may displace all other methods that use various organic solvents and catalysts and that are performed at high temperature. No organic solvents are used in this sequence, although extraction, heating, and column chromatography were carried out with ethyl acetate. The obtained results reveal water as the medium of choice for the examined Knoevenagel condensations and cycloaddition reactions.

All chemicals were purchased from Alfa-Aesar, Aldrich and Fluka and used without any further purification. Melting points were determined on a Boetius hot stage apparatus. IR spectra of samples in KBr pellets were recorded on a Bruker IFS 48. NMR spectra were recorded on a Bruker Avance II 300 (^{1}H: 300.18 MHz, ^{13}C: 75.48 MHz); samples were prepared in DMSO or $CDCl_3$ with TMS as an internal standard. Microanalyses were performed on a Euro EA 3000 Elemental Analyzer.

2-Thioxo-1,3-dihydropyrimidine-4,6-diones 3a–g; General Procedure for the Knoevenagel Condensation between 2-Thiobarbituric Acid 1a and Aldehydes 2a–g or Ketone 2j

The appropriate aldehyde **2a**–**g** or cyclopentanone (**2j**; 7 mmol) was added all at once to a stirred suspension of 2-thiobarbituric acid (**1a**; 1.00 g, 7 mmol) in distilled H_2O (50 mL) at r.t. The mixture was allowed to stir at r.t. for 1 h. The progress of the reaction was monitored by TLC ($CHCl_3$–MeOH, 1:1) until full consumption of the aldehyde. The thus formed precipitate of Knoevenagel products **3a**–**g** or **3n**,**o** was collected by filtration, washed with H_2O, and dried under vacuum. The compounds needed no further purification, but in some cases they were recrystallized from EtOAc; **3a**–**g** and **3n**,**o** were obtained in 88–95% yields. Compounds **3a**–**e** have been described previously: **3a**,[24a] **3b**,[24b] **3c**,[24c] **3d**,[24d] and **3e**.[24e] Spectroscopic data of compounds **3f**, **3g**, **3n**, and **3o** have not been reported before. Compounds **3h**–**m** were prepared by a published procedure.[17]

5-(2-Thienylmethylene)-2-thioxo-1,3-dihydropyrimidine-4,6-dione (3f)

Yellow crystals; mp 315 °C; yield: 1.52 g (91%).

IR (KBr): 3125 (NH), 3080 (CH), 1672 (C=O), 1569 (C=S), 1521 (C=C) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.38 (dd, *J* = 3.9, 5.1 Hz, 1 H, thienyl-H), 8.23 (ddd, *J* = 0.3, 1.2, 3.9 Hz, 1 H, thienyl-H), 8.35 (ddd, *J* = 1.2, 1.2, 5.1 Hz, 1 H, thienyl-H), 8.59 (s, 1 H, methylene-H), 12.36 (s, 1 H, NH), 12.38 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 111.7 (methylene-C), 128.6, 136.6, 143.1, 146.3 (C-2′, C-3′, C-4′, C-5′), 146.6 (C-5), 160.7 (C=O), 161.7 (C=O), 178.2 (C=S).

Anal. Calcd for $C_9H_6N_2O_2S_2$: C, 45.37; H, 2.54; N, 11.76; S, 26.91. Found: C, 45.41; H, 2.62; N, 11.79; S, 27.18.

5-(2-Furylmethylene)-2-thioxo-1,3-dihydropyrimidine-4,6-dione (3g)

Yellow crystals; mp >360 °C; yield: 1.48 g (95%).

IR (KBr): 3125 (NH), 3080 (CH), 1672 (C=O), 1569 (C=S), 1521 (C=C) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.96 (ddd, *J* = 0.6, 1.8, 3.6 Hz, 1 H, furyl-H), 8.05 (s, 1 H, methylene-H), 8.32 (dd, *J* = 0.6, 1.8 Hz, 1 H, furyl-H), 8.54 (dd, *J* = 0.6, 3.9 Hz, 1 H, furyl-H), 12.37 (s, 1 H, NH), 12.44 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 112.80, 115.53 (methylene-H), 127.45, 137.37, 150.39, 151.96 (C-2′, C-3′, C-4′, C-5′), 146.6 (C-5), 159.82 (C=O), 161.48 (C=O), 178.18 (C=S).

Anal. Calcd for $C_9H_6N_2O_3S$: C, 48.65; H, 2.72; N, 12.61; S, 14.43. Found: C, 48.91; H, 2.69; N, 12.78; S, 14.52.

5-Cyclopentylidene-2-thioxo-1,3-dihydropyrimidine-4,6-dione (3n)

Colorless crystals; mp 290 °C; yield: 1.37 g (93%).

IR (KBr): 3159 (N–H), 2947, 2882 (CH), 1705 (C=O), 1668 (C=S), 1572 (C=C) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.70 (dtt, *J* = 3.9, 7.2, 10.5 Hz, 4 H, H-3′), 3.08 (dtt, *J* = 4.5, 7.2, 9.9 Hz, 4 H, H-2′), 12.13 (s, 2 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 25.1 (C-3′), 38.8 (C-2′), 114.5 (C-1′), 160.9 (C-5), 177.9 (C=O), 193.0 (C=S).

Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.52; H, 4.75; N, 13.31; S, 15.55.

5-Cyclopentylidene-1,3-dimethylpyrimidine-2,4,6-trione (3o)

Colorless crystals; mp 113 °C; yield: 1.48 g (95%).

IR (KBr): 2972, 2883 (CH), 1727, 1665 (C=O), 1572 (C=C) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.81 (dtt, *J* = 3.3, 7.5, 15.0 Hz, 4 H, H-3′), 3.24 (dtt, *J* = 3.0, 7.5, 15.0 Hz, 4 H, H-2′), 3.34 (s, 6 H, N-CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 25.78 (C-3′), 28.28 (N-CH_3), 39.62 (C-2′), 100.88 (C-1′), 114.10 (C-5), 151.34 (C=O), 161.84 (C=O), 194.57 (C=O).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.46; H, 6.15; N, 12.67.

Pyrano[2,3-*d*]pyrimidines 5a–m; General Procedure for the Solvent-Free Hetero-Diels–Alder Cycloaddition

A mixture of one of Knoevenagel condensation products **3a**–**m** (4 mmol) with a tenfold excess of ethyl vinyl ether (**4**; 2.9 g, 3.8 mL, 40 mmol) was stirred without solvent at r.t. for 1–5 h. During stirring, solid compounds **3a**–**m** did not dissolve in the excess **4**, but a change in the color of the precipitate was observed, from yellow for dienes **3a**–**m** to colorless for cycloadducts **5a**–**m**. The progress of the reaction was monitored by TLC (EtOAc). The excess of ether was evaporated and the mixture was separated and purified by column chromatography (silica gel, EtOAc). Recrystallization (EtOAc–PE, 3:1) gave uracils **5a**–**m** in 88–96% yield (see Table 2).

Spirouracils 5n,o

A mixture of the appropriate compound **3n** or **3o** (4 mmol) with a tenfold excess of **4** (2.9 g, 3.8 mL, 40 mmol) was heated in EtOAc

(20 mL) at 77 °C in a pressure flask for 4 h. The progress of the reaction was monitored by TLC (EtOAc). The solvent and the excess ether was evaporated and the mixture was separated and purified by column chromatography (silica gel, EtOAc). Recrystallization (EtOAc–PE, 3:1) gave spirouracils **5n**,**o** in yields 88–91% (see Table 2).

Pyrano[2,3-*d*]pyrimidines 5a–k; General Procedure for the One-Pot Synthesis in Aqueous Suspension

A suspension of equimolar amounts (4 mmol) of one of barbituric acids **1a** or **1b** and the appropriate aromatic aldehyde **2a–i** with a tenfold excess of enol ether **4** (2.9 g, 3.8 mL, 40 mmol) in H_2O (50 mL) was allowed to stay under vigorous stirring at r.t. for 1–3 h. The progress of the reaction was monitored by TLC (EtOAc). After that, the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The mixture was separated and purified by column chromatography and the diastereoisomers were recrystallized by the procedure described above. During column chromatography, compounds were obtained in order of elution: **6a**,**b**, *trans*-**5a–k**, *cis*-**5a–k**. The total yields and ratios of **6a**,**b**, *trans*-**5a–k**, and *cis*-**5a–k** are given in Table 5.

(5*RS*,7*SR*)-7-Ethoxy-5-phenyl-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-5a)

Colorless crystals; mp 175 °C; yield: 0.638 g (60%); R_f = 0.56 (EtOAc).

IR (KBr) 3453, 3111 (NH), 3028, 2975, 2905 (CH), 1694 (C=O), 1647 (C=C), 1570 (C=C), 1247 (C=S), 1140, 1069 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.99 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.99 (ddd, *J* = 4.5, 5.1, 14.1 Hz, 1 H, 6-H), 2.29 (ddd, *J* = 2.7, 7.5, 14.1 Hz, 1 H, 6-H), 3.51 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.72 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.86 (dd, *J* = 5.1, 7.2 Hz, 1 H, H-5), 5.47 (dd, *J* = 2.7, 4.5 Hz, 1 H, H-7), 7.10–7.22 (m, 5 H, PhH), 12.12 (s, 1 H, NH), 12.86 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.7 (OCH_2CH_3), 32.2 (C-6), 35.0 (C-5), 64.2 (OCH_2CH_3), 92.9 (C-4a), 100.8 (C-7), 125.5, 127.3, 127.5, 143.5 (PhC), 155.9 (C-8a), 161.0 (C=O), 173.7 (C=S).

Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20; S, 10.53. Found: C, 59.23; H, 5.40; N, 9.14; S, 10.40.

(5*RS*,7*RS*)-7-Ethoxy-5-phenyl-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*trans*-5a)

Colorless crystals; mp 140 °C; yield: 0.304 g (28%); R_f = 0.68 (EtOAc).

IR (KBr): 3452, 3062 (NH), 2977, 2905 (CH), 1692 (C=O), 1648 (C=C), 1571 (C=C), 1248 (C=S), 1145, 1062 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 1.97 (ddd, *J* 2.4, 5.4, 13.8 Hz, 1 H, 6-H), 2.15 (ddd, *J* = 6.3, 7.5, 14.1 Hz, 1 H, 6-H), 3.64 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.84 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.87 (dd, *J* = 5.4, 6.3 Hz, 1 H, H-5), 5.19 (dd, *J* = 2.4, 7.5 Hz, 1 H, H-7), 7.16–7.30 (m, 5 H, PhH), 12.12 (s, 1 H, NH), 12.88 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.9 (OCH_2CH_3), 32.6 (C-6), 35.7 (C-5), 64.9 (OCH_2CH_3), 92.3 (C-4a), 99.9 (C-7), 126.1, 127.2, 128.2, 143.5 (PhC), 156.0 (C-8a), 161.0 (C=O), 173.9 (C=S).

Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20; S, 10.53. Found: C, 59.34; H, 5.33; N, 9.22; S, 10.71.

(5*RS*,7*SR*)-7-Ethoxy-5-(4-methoxyphenyl)-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-5b)

Colorless crystals; mp 314 °C; yield: 0.858 g (67%); R_f = 0.45 (EtOAc).

IR (KBr): 3435, 3110 (NH), 2973, 2904, 2836 (CH), 1694 (C=O), 1648 (C=C), 1572 (C=C), 1256 (C=S), 1141, 1045 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.02 (t, *J* = 7.05 Hz, 3 H, OCH_2CH_3), 1.93 (ddd, *J* = 4.8, 4.8, 14.1 Hz, 1 H, 6-H), 2.26 (ddd, *J* = 2.4, 7.2, 14.1 Hz, 1 H, 6-H), 3.69 (s, 3 H, OCH_3), 3.52 (dq, *J* = 7.2, 9.9 Hz, 1 H, OCH_2CH_3), 3.79 (dq, *J* = 7.2, 9.9 Hz, 1 H, OCH_2CH_3), 3.79 (dd, *J* = 4.8, 7.2 Hz, 1 H, H-5), 5.46 (dd, *J* = 2.4, 4.8 Hz, 1 H, H-7), 6.75 (d, *J* = 8.7 Hz, 2 H, ArH), 7.05 (d, *J* = 8.7 Hz, 2 H, ArH), 12.08 (s, 1 H, NH), 12.83 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.7 (OCH_2CH_3), 31.6 (C-6), 35.2 (C-5), 54.8 (OCH_3), 64.3 (OCH_2CH_3), 93.3 (C-4a), 100.9 (C-7), 112.9, 128.2, 135.5, 155.7 (ArC), 157.2 (C-8a), 160.9 (C=O), 173.7 (C=S).

Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.18; H, 5.42; N, 8.41; S, 9.67.

(5*RS*,7*RS*)-7-Ethoxy-5-(4-methoxyphenyl)-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*trans*-5b)

Colorless crystals; mp 130 °C; yield: 0.373 g (29%); R_f = 0.65 (EtOAc).

IR (KBr): 3466, 3134 (NH), 2974, 2902, 2839 (CH), 1693 (C=O), 1613 (C=C), 1562 (C=C), 1250 (C=S), 1176, 1040 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (t, *J* = 7.05 Hz, 3 H, OCH_2CH_3), 1.95 (ddd, *J* = 2.4, 4.8, 14.1 Hz, 1 H, 6-H), 2.10 (ddd, *J* = 6.6, 7.5, 13.5 Hz, 1 H, 6-H), 3.71 (s, 3 H, OCH_3), 3.64 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.85 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.83 (dd, *J* = 4.8, 6.6 Hz, 1 H, H-5), 5.16 (dd, *J* = 2.4, 7.5 Hz, 1 H, H-7), 6.82 (d, *J* = 8.7 Hz, 2 H, ArH), 7.08 (d, *J* = 8.7 Hz, 2 H, ArH), 12.10 (s, 1 H, NH), 12.86 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.9 (OCH_2CH_3), 31.8 (C-6), 35.8 (C-5), 54.9 (OCH_3), 64.9 (OCH_2CH_3), 92.5 (C-4a), 100.0 (C-7), 113.6, 128.2, 135.3, 155.9 (ArC), 157.6 (C-8a), 161.0 (C=O), 173.8 (C=S).

Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.48; H, 5.41; N, 8.32; S, 9.67.

(5*RS*,7*SR*)-5-(4-Cyanophenyl)-7-ethoxy-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-5c)

Colorless crystals; mp 175 °C; yield: 0.606 g (46%); R_f = 0.47 (EtOAc).

IR (KBr): 3413, 3097, 3052 (NH), 2973, 2907, 2869 (CH), 2226 (CN), 1681 (C=O), 1643 (C=C), 1577 (C=C), 1248 (C=S), 1140, 1069 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.95 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 2.05 (ddd, *J* = 3.9, 3.9, 14.4 Hz, 1 H, 6-H), 2.32 (ddd, *J* = 2.7, 7.5, 14.1 Hz, 1 H, 6-H), 3.49 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.69 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.94 (dd, *J* = 3.9, 7.2 Hz, 1 H, H-5), 5.50 (t, *J* = 3.0 Hz, 1 H, H-7), 7.37 (d, *J* = 8.1 Hz, 2 H, ArH), 7.65 (d, *J* = 8.4 Hz, 2 H, ArH), 12.20 (s, 1 H, NH), 12.94 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.58 (OCH_2CH_3), 31.19 (C-5), 33.90 (C-6), 64.19 (OCH_2CH_3), 91.80 (C-4a), 100.39 (C-7), 108.20 (CN), 119.02, 128.62, 131.39, 149.72 (ArC), 156.05 (C-8a), 161.12 (C=O), 173.93 (C=S).

Anal. Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.35; H, 4.59; N, 12.76; S, 9.73. Found: C, 58.42; H, 4.51; N, 12.91; S, 9.63.

(5*RS*,7*RS*)-5-(4-Cyanophenyl)-7-ethoxy-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*trans*-5c)

Colorless crystals; mp 175 °C; yield: 0.606 g (46%); R_f = 0.59 (EtOAc).

IR (KBr): 3415, 3100, 3049 (NH), 2971, 2902, 2859 (CH), 2219 (CN), 1683 (C=O), 1648 (C=C), 1572 (C=C), 1250 (C=S), 1139, 1062 (C–O) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 1.94 (ddd, *J* = 2.4, 6.9, 14.1 Hz, 1 H, 6-H), 2.19 (ddd, *J* = 6.3, 6.6, 14.1 Hz, 1 H, 6-H), 3.67 (dq, *J* = 7.2, 9.9 Hz, 1 H, OCH_2CH_3), 3.84 (dq, *J* = 7.2, 9.9 Hz, 1 H, OCH_2CH_3), 3.92 (t, *J* = 6.6, 6.6 Hz, 1 H, H-5), 5.29 (dd, *J* = 2.4, 6.3 Hz, 1 H, H-7), 7.44 (d, *J* = 8.1 Hz, 2 H, ArH), 7.72 (d, *J* = 8.4 Hz, 2 H, ArH), 12.15 (s, 1 H, NH), 12.93 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.88 (OCH_2CH_3), 32.59 (C-5), 35.22 (C-6), 64.84 (OCH_2CH_3), 91.88 (C-4a), 99.50 (C-7), 108.91 (CN), 118.83, 128.44, 132.06, 149.54 (ArC), 156.15 (C-8a), 160.88 (C=O), 173.98 (C=S).

Anal. Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.35; H, 4.59; N, 12.76; S, 9.73. Found: C, 58.29; H, 4.48; N, 12.68; S, 9.57.

(5*RS*,7*SR*)-5-(4-Chlorophenyl)-7-ethoxy-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-5d)
Colorless crystals; mp 175 °C; yield: 0.932 g (69%); R_f = 0.49 (EtOAc).

IR (KBr): 3415, 3135, 3063 (NH), 2978, 2913 (CH), 1682 (C=O), 1631 (C=C), 1561 (C=C), 1253 (C=S), 1217, 1134 (C–O) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.99 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 2.0 (ddd, *J* = 4.2, 4.2, 14.1 Hz, 1 H, 6-H), 2.28 (ddd, *J* = 2.7, 7.5, 14.1 Hz, 1 H, 6-H), 3.50 (dq, *J* = 7.2, 9.6 Hz, 1 H, OCH_2CH_3), 3.69 (dq, *J* = 7.2, 9.6 Hz, 1 H, OCH_2CH_3), 3.85 (dd, *J* = 4.2, 6.9 Hz, 1 H, H-5), 5.48 (dd, *J* = 2.7, 3.6 Hz, 1 H, H-7), 7.16 (d, *J* = 8.4 Hz, 2 H, ArH), 7.23 (d, *J* = 8.4 Hz, 2 H, ArH), 12.15 (s, 1 H, NH), 12.89 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.64 (OCH_2CH_3), 31.39 (C-5), 34.41 (C-6), 64.21 (OCH_2CH_3), 92.45 (C-4a), 100.58 (C-7), 127.32, 129.27, 129.89, 142.63 (ArC), 155.89 (C-8a), 161.04 (C=O), 173.81 (C=S).

Anal. Calcd for $C_{15}H_{15}ClN_2O_3S$: C, 53.18; H, 4.46; N, 8.27; S, 9.46. Found: C, 53.27; H, 4.59; N, 8.16; S, 9.74.

(5*RS*,7*RS*)-5-(4-Chlorophenyl)-7-ethoxy-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*trans*-5d)
Colorless crystals; mp 135 °C; yield: 0.274 g (20%); R_f = 0.61 (EtOAc).

IR (KBr): 3412, 3062 (NH), 2977, 2910 (CH), 1684 (C=O), 1632 (C=C), 1563 (C=C), 1252 (C=S), 1218, 1135 (C–O) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.05 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.93 (ddd, *J* = 2.4, 5.7, 14.1 Hz, 1 H, 6-H), 2.15 (ddd, *J* = 6.3, 7.2, 14.1 Hz, 1 H, 6-H), 3.52 (dq, *J* = 7.2, 9.6 Hz, 1 H, OCH_2CH_3), 3.70 (dq, *J* = 7.2, 9.6 Hz, 1 H, OCH_2CH_3), 3.71 (dd, *J* = 5.7, 7.2 Hz, 1 H, H-5), 5.23 (dd, *J* = 2.4, 6.6 Hz, 1 H, H-7), 7.29 (d, *J* = 8.4 Hz, 2 H, ArH), 7.31 (d, *J* = 8.4 Hz, 2 H, ArH), 12.13 (s, 1 H, NH), 12.89 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.87 (OCH_2CH_3), 31.96 (C-5), 35.48 (C-6), 64.85 (OCH_2CH_3), 92.14 (C-4a), 99.70 (C-7), 128.03, 129.15, 130.62, 142.51 (ArC), 156.04 (C-8a), 160.92 (C=O), 173.93 (C=S).

Anal. Calcd for $C_{15}H_{15}ClN_2O_3S$: C, 53.18; H, 4.46; N, 8.27; S, 9.46. Found: C, 53.29; H, 4.38; N, 8.32; S, 9.57.

(5*RS*,7*SR*)-5-(4-Bromophenyl)-7-ethoxy-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-5e)
Colorless crystals; mp 314 °C; yield: 1.039 g (68%); R_f = 0.45 (EtOAc).

IR (KBr): 3408, 3062 (NH), 2977, 2905 (CH), 1690 (C=O), 1631 (C=C), 1562 (C=C), 1242 (C=S), 1217, 1133 (C–O) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.99 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 1.98 (ddd, *J* = 3.9, 4.2, 14.4 Hz, 1 H, 6-H), 2.28 (ddd, *J* = 2.7, 7.5, 14.4 Hz, 1 H, 6-H), 3.50 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.71 (dq, *J* = 7.2, 9.6 Hz, 1 H, OCH_2CH_3), 3.84 (dd, *J* = 4.5, 7.2 Hz, 1 H, H-5), 5.48 (dd, *J* = 2.7, 3.9 Hz, 1 H, H-7), 7.12 (d, *J* = 8.4 Hz, 2 H, ArH), 7.36 (d, *J* = 8.7 Hz, 2 H, ArH), 12.15 (s, 1 H, NH), 12.89 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.65 (OCH_2CH_3), 31.39 (C-5), 34.37 (C-6), 64.21 (OCH_2CH_3), 92.40 (C-4a), 100.56 (C-7), 118.33, 127.32, 129.28, 129.71, 130.24, 143.10 (ArC), 155.93 (C-8a), 161.04 (C=O), 173.81 (C=S).

Anal. Calcd for $C_{15}H_{15}BrN_2O_3S$: C, 47.01; H, 3.94; N, 7.31; S, 8.37. Found: C, 47.12; H, 4.01; N, 7.32; S, 8.41.

(5*RS*,7*RS*)-5-(4-Bromophenyl)-7-ethoxy-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*trans*-5e)
Colorless crystals; mp 314 °C; yield: 0.371 g (24%); R_f = 0.64 (EtOAc).

IR (KBr): 3392, 3135 (NH), 2977, 2902 (CH), 1680 (C=O), 1647 (C=C), 1570 (C=C), 1244 (C=S), 1217, 1126 (C–O) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.93 (ddd, *J* = 2.1, 6.0, 14.1 Hz, 1 H, 6-H), 2.15 (ddd, *J* = 6.3, 6.9, 14.1 Hz, 1 H, 6-H), 3.66 (dq, *J* = 7.2, 9.6 Hz, 1 H, OCH_2CH_3), 3.84 (dq, *J* = 6.9, 9.9 Hz, 1 H, OCH_2CH_3), 3.84 (dd, *J* = 6.6, 6.6 Hz, 1 H, H-5), 5.23 (dd, *J* = 2.1, 6.9 Hz, 1 H, H-7), 7.17 (d, *J* = 8.4 Hz, 2 H, ArH), 7.43 (d, *J* = 8.4 Hz, 2 H, ArH), 12.13 (s, 1 H, NH), 12.90 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.88 (OCH_2CH_3), 32.02 (C-5), 35.44 (C-6), 64.86 (OCH_2CH_3), 92.08 (C-4a), 99.69 (C-7), 119.09, 128.03, 129.15, 129.56, 130.95, 142.96 (ArC), 156.05 (C-8a), 160.92 (C=O), 173.92 (C=S).

Anal. Calcd for $C_{15}H_{15}BrN_2O_3S$: C, 47.01; H, 3.94; N, 7.31; S, 8.37. Found: C, 47.18; H, 3.98; N, 7.16; S, 8.66.

(5*RS*,7*SR*)-7-Ethoxy-5-(2-thienyl)-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-5f)
Colorless crystals; mp 135 °C; yield: 0.447 g (36%); R_f = 0.49 (EtOAc).

IR (KBr): 3416, 3106 (NH), 2976, 2894 (CH), 1694 (C=O), 1645 (C=C), 1569 (C=C), 1249 (C=S), 1216, 1140 (C–O) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.01 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 2.14 (ddd, *J* = 3.3, 3.6, 14.4 Hz, 1 H, 6-H), 2.32 (ddd, *J* = 3.0, 6.9, 14.4 Hz, 1 H, 6-H), 3.53 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.71 (dq, *J* = 7.2, 9.9 Hz, 1 H, OCH_2CH_3), 4.14 (dd, *J* = 3.6, 6.9 Hz, 1 H, H-5), 5.52 (dd, *J* = 3.0, 3.3 Hz, 1 H, H-7), 6.83–6.89 (m, 2 H, thienyl-H), 7.20 (dd, *J* = 2.1, 4.5 Hz, 1 H, thienyl-H), 12.18 (s, 1 H, NH), 12.88 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.64 (OCH_2CH_3), 27.10 (C-5), 34.60 (C-6), 64.26 (OCH_2CH_3), 93.36 (C-4a), 100.24 (C-7), 122.70, 124.06, 125.96, 147.76 (thienyl-C), 155.22 (C-8a), 160.96 (C=O), 173.78 (C=S).

Anal. Calcd for $C_{13}H_{14}N_2O_3S_2$: C, 50.31; H, 4.55; N, 9.03; S, 20.66. Found: C, 50.38; H, 4.72; N, 8.71; S, 20.45.

(5*RS*,7*RS*)-7-Ethoxy-5-(2-thienyl)-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*trans*-5f)
Colorless crystals; mp 140 °C; yield: 0.67 g (54%); R_f = 0.60 (EtOAc).

IR (KBr): 3413, 3068 (NH), 2975, 2897 (CH), 1694 (C=O), 1629 (C=C), 1559 (C=C), 1247 (C=S), 1218, 1137 (C–O) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.16 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 2.14 (ddd, *J* = 5.1, 5.4, 10.5 Hz, 2 H, 6-H), 3.67 (dq, *J* = 6.9, 9.6 Hz, 1 H, OCH_2CH_3), 3.88 (dq, *J* = 7.2, 9.9 Hz, 1 H,

OCH_2CH$_3$), 4.16 (dd, J = 4.2, 5.1 Hz, 1 H, H-5), 5.25 (dd, J = 5.4, 5.7 Hz, 1 H, H-7), 6.90 (ddd, J = 0.9, 1.5, 3.0 Hz, 1 H, thienyl-H), 6.93 (dd, J = 3.0, 8.4 Hz, 1 H, thienyl-H), 7.33 (dd, J = 1.5, 5.1 Hz, 1 H, thienyl-H), 12.20 (s, 1 H, NH), 12.91 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.87 (OCH$_2$*C*H$_3$), 28.29 (C-5), 35.46 (C-6), 65.09 (O*C*H$_2$CH$_3$), 92.71 (C-4a), 100.37 (C-7), 123.89, 124.51, 126.93, 147.24 (thienyl-C), 155.63 (C-8a), 160.95 (C=O), 173.99 (C=S).

Anal. Calcd for $C_{13}H_{14}N_2O_3S_2$: C, 50.31; H, 4.55; N, 9.03; S, 20.66. Found: C, 50.47; H, 4.76; N, 8.71; S, 20.49.

(5*RS*,7*SR*)-7-Ethoxy-5-(2-furyl)-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-5g)

Colorless crystals; mp 295 °C; yield: 0.524 g (44.5%); R_f = 0.47 (EtOAc).

IR (KBr): 3414, 3112 (NH), 2972, 2896 (CH), 1691 (C=O), 1648 (C=C), 1559 (C=C), 1248 (C=S), 1212, 1138 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.97 (t, J = 6.9 Hz, 3 H, OCH$_2$C*H*$_3$), 2.13 (ddd, J = 3.0, 6.9, 14.1 Hz, 1 H, 6-H), 2.24 (ddd, J = 3.3, 3.6, 14.1 Hz, 1 H, 6-H), 3.52 (dq, J = 6.9, 9.6 Hz, 1 H, OC*H*$_2$CH$_3$), 3.69 (dq, J = 6.9, 9.6 Hz, 1 H, OC*H*$_2$CH$_3$), 3.94 (dd, J = 3.9, 6.9 Hz, 1 H, H-5), 5.51 (dd, J = 2.7, 3.0 Hz, 1 H, H-7), 5.89 (ddd, J = 0.9, 0.9, 3.3 Hz, 1 H, furyl-H), 6.25 (dd, J = 1.8, 3.3 Hz, 1 H, furyl-H), 7.40 (dd, J = 0.9, 2.0 Hz, 1 H, furyl-H), 12.18 (s, 1 H, NH), 12.85 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.61 (OCH$_2$*C*H$_3$), 25.35 (C-5), 30.57 (C-6), 64.08 (O*C*H$_2$CH$_3$), 91.14 (C-4a), 100.02 (C-7), 104.68, 110.14, 140.18, 155.38 (furyl-C), 155.46 (C-8a), 161.04 (C=O), 173.85 (C=S).

Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52; S, 10.89. Found: C, 53.35; H, 4.82; N, 9.63; S, 10.93.

(5*RS*,7*RS*)-7-Ethoxy-5-(2-furyl)-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*trans*-5g)

Colorless crystals; mp 305 °C; yield: 0.524 g (44.5%); R_f = 0.65 (EtOAc).

IR (KBr): 3409, 3059 (NH), 2981, 2892 (CH), 1691 (C=O), 1635 (C=C), 1558 (C=C), 1249 (C=S), 1216, 1131 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.05 (t, J = 6.9 Hz, 3 H, OCH$_2$C*H*$_3$), 2.07 (ddd, J = 2.4, 6.6, 14.1 Hz, 1 H, 6-H), 2.12 (ddd, J = 6.3, 7.2, 14.1 Hz, 1 H, 6-H), 3.68 (dq, J = 6.9, 9.6 Hz, 1 H, OC*H*$_2$CH$_3$), 3.86 (dq, J = 6.9, 9.6 Hz, 1 H, OC*H*$_2$CH$_3$), 3.85 (dd, J = 6.3, 6.6 Hz, 1 H, H-5), 5.23 (dd, J = 2.4, 7.5 Hz, 1 H, H-7), 6.11 (ddd, J = 0.9, 0.9, 3.3 Hz, 1 H, furyl-H), 6.33 (dd, J = 1.8, 3.3 Hz, 1 H, furyl-H), 7.51 (dd, J = 0.9, 1.8 Hz, 1 H, furyl-H), 12.16 (s, 1 H, NH), 12.85 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.86 (OCH$_2$*C*H$_3$), 27.07 (C-5), 30.80 (C-6), 65.08 (O*C*H$_2$CH$_3$), 90.45 (C-4a), 100.58 (C-7), 106.22, 110.35, 141.59, 155.18 (furyl-C), 155.18 (C-8a), 160.92 (C=O), 174.01 (C=S).

Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52; S, 10.89. Found: C, 53.16; H, 4.70; N, 9.58; S, 10.81.

(7′*RS*)-7′-Ethoxy-2′-thioxospiro[cyclopentane-1,5′-{1′,5′,6′,7′-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4′(3′*H*)-one}] (5n)

Colorless crystals; mp 217 °C; yield: 0.993 g (88%); R_f = 0.64 (EtOAc).

IR (KBr): 3414, 3204 (NH), 2971, 2932, 2873 (CH), 1643 (C=O), 1550 (C=C), 1336 (C=S), 1152, 1055 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.1 (t, J = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$), 1.32–1.39 (m, 1 H, cyclopentane-H), 1.42–1.49 (m, 1 H, cyclopentane-H), 1.58–1.64 (m, 4 H, cyclopentane-H), 1.70 (dd, J = 6.9, 13.5 Hz, 1 H, H-6′), 1.89 (dd, J = 2.1, 14.1 Hz, 1 H, H-6′), 2.05 (ddd, J = 4.2, 7.8, 12.0 Hz, 1 H, cyclopentane-H), 2.22 (ddd, J = 2.7, 8.1, 12.3 Hz, 1 H, cyclopentane-H), 3.67 (dq, J = 6.9, 9.6 Hz, 1 H, OC*H*$_2$CH$_3$), 3.84 (dq, J = 6.9, 9.6 Hz, 1 H, OC*H*$_2$CH$_3$), 5.29 (dd, J = 2.1, 6.9 Hz, 1 H, H-7′), 12.01 (s, 1 H, NH), 12.66 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.89 (OCH$_2$*C*H$_3$), 24.28, 24.61, 37.54 (cyclopentane-H), 35.52 (C-6′), 64.69 (O*C*H$_2$CH$_3$), 96.98 (C-4′a), 100.71 (C-7′), 154.72 (C-8′a), 160.80 (C=O), 172.98 (C=S).

Anal. Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43; N, 9.92; S, 11.35. Found: C, 55.25; H, 6.52; N, 9.79; S, 11.45.

(7′*RS*)-7′-Ethoxy-1′,3′-dimethylspiro[cyclopentane-1,5′-{1′,5′,6′,7′-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2′,4′(3′*H*)-dione}] (5o)

Colorless oil; yield: 1.071 g (91%); R_f = 0.59 (EtOAc).

IR (KBr): 2955, 2873 (CH), 1704, 1645 (C=O), 1613 (C=C), 1178 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.24 (t, J = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$), 1.38–1.87 (m, 6 H, cyclopentane-H), 1.72 (dd, J = 8.1, 13.8 Hz, 1 H, H-6′), 1.93 (dd, J = 2.1, 13.8 Hz, 1 H, H-6′), 2.16 (ddd, J = 3.9, 8.7, 12.6 Hz, 1 H, cyclopentane-H), 2.37 (ddd, J = 3.0, 6.9, 12.6 Hz, 1 H, cyclopentane-H), 3.25 (s, 3 H, N-CH$_3$), 3.30 (s, 3 H, N-CH$_3$), 3.65 (dq, J = 7.2, 9.6 Hz, 1 H, OC*H*$_2$CH$_3$), 3.93 (dq, J = 7.2, 9.6 Hz, 1 H, OC*H*$_2$CH$_3$), 5.08 (dd, J = 2.1, 8.1 Hz, 1 H, H-7′).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.95 (OCH$_2$*C*H$_3$), 25.12, 25.50, 36.93, 38.82, 40.33 (cyclopentane-C), 27.58 (N-CH$_3$), 28.56 (N-CH$_3$), 41.70 (C-6′), 65.63 (O*C*H$_2$CH$_3$), 93.66 (C-4′a), 101.82 (C-7′), 150.85 (C-8′a), 153.73 (C=O), 161.69 (C=O).

Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.29; H, 7.62; N, 9.47.

7-Ethoxy-5-methyl-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (6a)

Colorless crystals; mp 200 °C; R_f = 0.75 (EtOAc).

IR (KBr): 3479, 3150 (NH), 3059, 2978, 2901 (CH), 1680 (C=O), 1621 (C=C), 1248 (C=S), 1156, 1135, 1033 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.15 (dd, J = 4.5, 6.9 Hz, 3 H, 5-CH$_3$), 1.20 (t, J = 6.9 Hz, 3 H, OCH$_2$C*H*$_3$), 1.69–1.79 (m, 0.8 H, 6-H), 1.85 (dd, J = 7.2, 14.4 Hz, 0.8 H, 6-H), 2.02 (ddd, J = 3.0, 7.2, 14.4 Hz, 0.4 H, 6-H), 2.59–2.71 (m, 1 H, H-5), 3.70 (dq, J = 6.9, 10.8 Hz, 1 H, OC*H*$_2$CH$_3$), 3.86 (dq, J = 7.2, 9.9 Hz, 1 H, OC*H*$_2$CH$_3$), 5.43 (dd, J = 2.4, 7.2 Hz, 0.6 H, H-7), 5.47 (dd, J = 3.0, 3.3 Hz, 0.4 H, H-7), 12.07 (s, 1 H, NH), 12.69 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.91 (OCH$_2$*C*H$_3$), 19.39 (5-CH$_3$), 21.27, 21.70 (C-6), 32.51, 33.95 (C-5), 64.58, 64.74 (O*C*H$_2$CH$_3$), 95.18, 95.38 (C-4a), 99.93, 100.66 (C-7), 154.18, 154.72 (C-8a), 161.46, 161.52 (C=O), 173.31, 173.42 (C=S).

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56; S, 13.23. Found: C, 49.78; H, 5.79; N, 11.23; S, 13.48.

7-Ethoxy-1,3,5-trimethyl-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2,4(3*H*)-dione (6b)

Colorless oil; R_f = 0.72 (EtOAc).

IR (KBr): 3046, 2985, 2899 (CH), 1705, 1652 (C=O), 1549 (C=C), 1152, 1129, 1058 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, J = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$), 1.28 (dd, J = 4.5, 7.2 Hz, 3 H, 5-CH$_3$), 1.86–1.94 (m, 0.8 H, 6-H), 2.04 (dd, J = 6.9, 14.1 Hz, 0.8 H, 6-H), 2.35 (ddd, J = 3.2, 7.0, 14.1 Hz, 0.4 H, 6-H), 2.61–2.72 (m, 1-H, H-5), 3.29 (s, 3 H, N-CH$_3$), 3.42 (s, 3 H, N-CH$_3$), 3.65 (dq, J = 7.2, 10.0 Hz, 1 H,

OCH_2CH_3), 3.87 (dq, J = 7.2, 9.9 Hz, 1 H, OCH_2CH_3), 5.30 (dd, J = 3.0, 7.8 Hz, 0.6 H, H-7), 5.40 (dd, J = 3.0, 3.3 Hz, 0.4 H, H-7).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.89 (OCH_2CH_3), 20.12 (5-CH_3), 22.60, 23.18 (C-6), 27.86 (N-CH_3), 28.67 (N-CH_3), 33.30, 33.67 (C-5), 65.90, 65.99 (OCH_2CH_3), 91.57, 91.95 (C-4a), 101.23, 101.84 (C-7), 151.23, 151.38 (C-8a), 153.94, 162.16, 162.62, 162.75 (C=O).

Anal. Calcd for $C_{12}H_1N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.92; H, 7.24; N, 11.13.

Pyrano[2,3-*d*]pyrimidines 8a–h; General Procedure for the One-Pot Synthesis in Aqueous Suspension

A suspension of equimolar amounts (4 mmol) of one of barbituric acids **1a** or **1b**, the appropriate aromatic aldehyde **2a** or **2h**, and styrene **7a** or *N*-vinyl-2-oxazolidinone **7b** in H_2O (50 mL) was stirred at 60 °C for 1–3 h. The progress of the reaction was monitored by TLC (EtOAc). After that, the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude products were purified by column chromatography (silica gel, EtOAc). Recrystallization (EtOAc–PE, 4:1) gave uracils *cis*-**8a**–**h** in 89–95% yields (see Table 8).

(5*RS*,7*SR*)-7-(4-Methoxyphenyl)-5-phenyl-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-8a)

Colorless crystals; mp 196 °C; yield: 1.304 g (89%); R_f = 0.51 (EtOAc).

IR (KBr) 3451, 3130 (NH), 3032, 2981, 2904 (CH), 1687 (C=O), 1647 (C=C), 1565 (C=C), 1249 (C=S), 1138, 1073 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.03 (ddd, J = 11.3, 11.3, 14.4 Hz, 1 H, 6-H), 2.45 (ddd, J = 1.8, 6.3, 14.1 Hz, 1 H, 6-H), 3.83 (s, 3 H, OCH_3), 3.96 (dd, J = 6.6, 11.3 Hz, 1 H, H-5), 5.49 (dd, J = 1.8, 11.3 Hz, 1 H, H-7), 7.10–7.92 (m, 9 H, PhH), 12.10 (s, 1 H, NH), 12.92 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 32.0 (C-6), 34.8 (C-5), 81.8 (C-7), 93.2 (C-4a), 125.5, 126.4, 127.3, 127.5, 128.4, 129.1 143.5, 144.6 (PhC), 156.8 (C-8a), 161.7 (C=O), 174.1 (C=S).

Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C, 65.56; H, 4.95; N, 7.64; S, 8.75. Found: C, 65.82; H, 4.81; N, 7.82; S, 8.69.

(5*RS*,7*SR*)-7-(4-Methoxyphenyl)-5-(4-nitrophenyl)-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-8b)

Colorless crystals; mp 212 °C; yield: 1.547 g (94%); R_f = 0.49 (EtOAc).

IR (KBr) 3448, 3127 (NH), 3029, 2983, 2901 (CH), 1678 (C=O), 1641 (C=C), 1569 (C=C), 1253 (C=S), 1139, 1068 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.09 (ddd, J = 11.1, 11.3, 14.2 Hz, 1 H, 6-H), 2.47 (ddd, J = 1.6, 6.5, 14.1 Hz, 1 H, 6-H), 3.81 (s, 3 H, OCH_3), 4.10 (dd, J = 6.5, 11.1 Hz, 1 H, H-5), 5.51 (dd, J = 2.0, 11.3 Hz, 1 H, H-7), 6.90–8.22 (m, 8 H, PhH), 12.11 (s, 1 H, NH), 12.91 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 31.9 (C-6), 35.2 (C-5), 82.3 (C-7), 93.1 (C-4a), 125.7, 127.3, 128.5, 129.7 143.7, 144.9, 151.06, 151.57 (PhC), 157.1 (C-8a), 162.1 (C=O), 174.3 (C=S).

Anal. Calcd for $C_{20}H_{17}N_3O_5S$: C, 58.39; H, 4.16; N, 10.21; S, 7.79. Found: C, 58.42; H, 4.35; N, 10.37; S, 7.86.

(5*RS*,7*SR*)-7-(2-Oxooxazolidin-3-yl)-5-phenyl-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-8c)

Colorless crystals; mp 235 °C; yield: 1.257 g (91%); R_f = 0.56 (EtOAc).

IR (KBr) 3449, 3135 (NH), 3031, 2985, 2901 (CH), 1765 (C=O), 1686 (C=O), 1645 (C=C), 1561 (C=C), 1241 (C=S), 1135, 1069 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.07 (ddd, J = 11.0, 11.4, 14.2 Hz, 1 H, 6-H), 2.41 (ddd, J = 2.0, 6.5, 14.1 Hz, 1 H, 6-H), 3.55 (dt, J = 5.0, 8.5 Hz, 1 H, H-4′), 3.63 (q, J = 8.5 Hz, 1 H, H-4′), 4.05 (dd, J = 6.3, 11.0 Hz, 1 H, H-5), 4.28 (q, J = 8.5 Hz, 1 H, H-5′), 4.40 (dt, J = 5.0, 8.5 Hz, 1 H, H-5′), 5.91 (dd, J = 1.8, 11.1 Hz, 1 H, H-7), 7.33–7.75 (m, 5 H, PhH), 12.09 (s, 1 H, NH), 12.87 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.4 (C-6), 34.7 (C-5), 87.5 (C-7), 87.2 (C-4a), 125.7, 127.5, 128.6, 143.9 (PhC), 155.9 (C-8a), 161.5 (C=O), 161.9 (C-2′), 174.7 (C=S).

Anal. Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17; S, 9.28. Found: C, 55.77; H, 4.35; N, 12.28; S, 9.43.

(5*RS*,7*SR*)-5-(4-Nitrophenyl)-7-(2-oxooxazolidin-3-yl)-2-thioxo-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (*cis*-8d)

Colorless crystals; mp 263 °C; yield: 1.437 g (92%); R_f = 0.53 (EtOAc).

IR (KBr) 3447, 3139 (NH), 3038, 2981, 2912 (CH), 1768 (C=O), 1686 (C=O), 1649 (C=C), 1557 (C=C), 1245 (C=S), 1139, 1072 (C–O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.10 (ddd, J = 11.1, 11.3, 14.1 Hz, 1 H, 6-H), 2.39 (ddd, J = 1.8, 6.3, 14.2 Hz, 1 H, 6-H), 3.57 (dt, J = 5.0, 8.5 Hz, 1 H, H-4′), 3.63 (q, J = 8.5 Hz, 1 H, H-4′), 4.09 (dd, J = 6.5, 11.3 Hz, 1 H, H-5), 4.30 (q, J = 8.5 Hz, 1 H, H-5′), 4.45 (dt, J = 5.0, 8.5 Hz, 1 H, H-5′), 5.96 (dd, J = 2.1, 11.0 Hz, 1 H, H-7), 7.40 (d, J = 9.0 Hz, 2 H, ArH), 8.20 (d, J = 9.0 Hz, 2 H, ArH), 12.10 (s, 1 H, NH), 12.85 (s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 32.8 (C-6), 35.0 (C-5), 88.2 (C-7), 87.3 (C-4a), 124.0, 127.9, 129.6, 149.7 (ArC), 155.6 (C-8a), 162.1 (C=O), 162.5 (C-2′), 174.5 (C=S).

Anal. Calcd for $C_{16}H_{14}N_4O_6S$: C, 49.23; H, 3.61; N, 14.35; S, 8.21. Found: C, 49.45; H, 3.67; N, 14.27; S, 8.46.

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References

(1) (a) Rideout, D. S.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Narayan, S.; Muldoon, J. M.; Finn, G. V.; Fokin, V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.
(2) Jovanovic, M. V.; Biel, E. R. *J. Org. Chem.* **1987**, *24*, 191.
(3) Haldar, M. K.; Scott, M. D.; Sule, N.; Srivastava, D. K.; Mallik, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2373.
(4) Kitamura, N.; Onishi, A. EP 163599, **1984**; *Chem. Abstr.* **1984**, *104*, 186439.
(5) Furuja, S.; Ohtaki, T. EP Application 608565, **1994**; *Chem. Abstr.* **1994**, *121*, 205395.
(6) Heber, D.; Heers, C.; Ravens, U. *Pharmazie* **1993**, *48*, 537.
(7) Coates, W. EP 351058, **1990**; *Chem. Abstr.* **1990**, *113*, 40711.
(8) Sakuma, Y.; Hasegawa, M.; Kataoka, K.; Hoshina, K.; Yamazaki, N.; Kadota, T.; Yamaguchi, H. WO Application 9105785, **1989**; *Chem. Abstr.* **1989**, *115*, 71646.
(9) Anderson, G. L.; Shim, J. L.; Broom, A. D. *J. Org. Chem.* **1976**, *41*, 1095.

(10) (a) Ahluvalia, V. K.; Sharma, H. R.; Tyagi, R. *Tetrahedron* **1986**, *42*, 4045. (b) Wamhoff, H.; Muhr, J. *Synthesis* **1988**, 919. (c) Ahluwalia, V. K.; Kumar, R.; Khurana, K.; Batla, R. *Tetrahedron* **1990**, *46*, 3953. (d) Hirota, K.; Kuki, H.; Maki, Y. *Heterocycles* **1994**, *37*, 563. (e) Srivastava, P.; Saxena, A. S.; Ram, V. J. *Synthesis* **2000**, 541.
(11) Devi, I.; Kumar, B. S. D.; Bhuyan, P. J. *Tetrahedron Lett.* **2003**, *44*, 8307.
(12) Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 7727.
(13) Devi, I.; Borah, H. N.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 2405.
(14) Naya, S.; Miyagawa, M.; Nitta, M. *Tetrahedron* **2005**, *61*, 4919.
(15) (a) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1997**, *45*, 1715. (b) Binev, I. G.; Binev, Y. G.; Stamboliyska, B. A.; Juchnovski, I. N. *J. Mol. Struct.* **1997**, *435*, 235. (c) Ayoubi, S. A.; Texier-Boullet, F.; Hamelin, J. *Synthesis* **1994**, 258.
(16) Jursic, B. S.; Stevens, E. D. *Tetrahedron Lett.* **2003**, *44*, 2203.
(17) Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2005**, *46*, 6453.
(18) Pałasz, A. *Monatsh. Chem.* **2008**, *139*, 1397.
(19) Bushweller, C. H.; O'Neil, J. W. *Tetrahedron Lett.* **1969**, 4713.
(20) Sankararaman, S. *Pericyclic Reactions – A Textbook*; Wiley-VCH: Weinheim, **2005**.
(21) (a) Tietze, L. F.; Meier, H.; Nutt, H. *Chem. Ber.* **1989**, *122*, 643. (b) Tietze, L. F.; Stegelmeier, H.; Harms, K.; Brumby, T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 863. (c) Tietze, L. F.; Brumby, T.; Brand, S.; Bratz, M. *Chem. Ber.* **1988**, *121*, 499. (d) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. *Synthesis* **1994**, 1185. (e) Tietze, L. F.; Brand, S.; Pfeiffer, T.; Antel, J. J.; Harms, K.; Sheldrick, G. M. *J. Am. Chem. Soc.* **1987**, *109*, 921. (f) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (g) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, **2006**. (h) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1.
(22) Bogdanowicz-Szwed, K.; Pałasz, A. *Z. Naturforsch., B* **2001**, *56*, 416.
(23) Pałasz, A. *Org. Biomol. Chem.* **2005**, *3*, 3207.
(24) (a) Hu, Y.; Chen, Z. C.; Le, Z. G.; Zheng, Q. G. *Synth. Commun.* **2004**, *34*, 4521. (b) Wang, C.; Ma, J.; Zhou, X.; Zang, X.; Wang, Z.; Gao, Y.; Cui, P. *Synth. Commun.* **2005**, *35*, 2759. (c) Medien, H. A. A.; Zahran, A. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1069. (d) Shi, D. Q.; Chen, J.; Zhuang, Q. Y.; Wang, X. S.; Hu, H. W. *Chin. Chem. Lett.* **2003**, *14*, 1242. (e) Moskvin, A. V.; Polkovnikova, I. I.; Ivin, B. A. *Russ. J. Gen. Chem.* **1998**, *68*, 801.