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Full Paper

An Efficient One-pot Two-component Protocol for Regio- and Chemoselective Synthesis of 5-Aryloyl-1,3,7,9-tetraalkyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-diones

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Novel symmetric fused pyrano[2,3-*d*]pyrimidine derivatives were synthesized in 75–92 % yield by a one-pot two-component reaction of arylglyoxals and 1,3-dialkyl-2-thiobarbituric acids in ethanol at room temperature. This is the first protocol to be reported for the synthesis of 5-aryloyl-1,3,7,9-tetraalkyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-diones and the significant features of the present protocol are simplicity, high yields, a simple isolation procedure, and high chemoselectivity.

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Introduction

Pyrane and its derivatives have attracted great interest owing to the incorporation of this ring system in compounds showing antimicrobial,[1–3] influenza inhibition, virus sialidase,[4] mutagenic,[5] antiviral,[6] antiproliferation,[7] sex-pheromone,[8] antitumour,[9] and anti-inflammatory activity.[10] Moreover, pyrane derivatives are well known for their antihistaminic activity.[11] Also, pyrimidines and their fused derivatives play an essential role in several biological processes of chemical and pharmacological importance. In particular, the pyrimidine nucleus can be found in a broad variety of antibacterial, antiviral, NAR (nicotinic acid receptor), and antitumour agents as well as in agrochemical and veterinary products.[12–15] Examples of such compounds are emivirine and 5-ethyl-2-thioxo-2,3-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine pyrano[2,3-*d*]pyrimidine-4,7-dione (Fig. 1.).[16,17]

Designing new multicomponent reactions (MCRs) as well as improving known MCRs constitutes a research area of immense interest in contemporary organic synthesis.[18] In contrast to classical multistep linear synthetic protocols, MCRs enable expedient and efficient assembly of molecules of structural complexity and diversity in one-pot operations with facile execution, and high atom economy and selectivity.[18b,18c,19,20] These reactions obviate the isolation and purification of intermediates and diminish waste generation, thereby enhancing the greenness of transformations. Consequently, MCRs have emerged as a powerful tool for delivering molecular libraries needed in combinatorial approaches for the assembly and lead identification of bioactive compounds.[21]

Based on the above considerations and in continuance of our previous research into the arylglyoxal-mediated synthesis of various heterocycles,[22–32] we have found that 1,3-dialkyl thiobarbituric acids undergo a tandem Knoevenagel–Michael condensation with arylglyoxals leading to the formation of a substituted pyranopyrimidine skeleton. Herein, we report an efficient two-component strategy for synthesis of symmetrically substituted 5-aryloyl-1*H*-pyrano[2,3-*d*]pyrimidine **1**. The retrosynthesis of this novel strategy is shown in Scheme 1.

Results and Discussion

During our recent work on the synthesis of new pyrimidopyridazine derivatives,[22] we found that in some cases stirring the mixture of 1,3-diethyl-2-thiobarbituric acid or 1,3-dimethyl-2-thiobarbituric acid and arylglyoxals with hydrazine in ethanol at room temperature led to the formation of insoluble intermediates that did not react with the hydrazine. We have now investigated these reactions in the absence of hydrazine and have characterized the products as previously unreported pyranopyrimidine derivatives.

The arylglyoxal derivatives (**2a**–**j**) react with two equivalents of 1,3-diethyl-2-thiobarbituric acid (**3a**) or 1,3-dimethyl-2-thiobarbituric acid (**3b**) in ethanol at room temperature to produce symmetric pyrano[2,3-*d*]pyrimidine derivatives **1a**–**s** that partially exist as the enol tautomers **4a**–**s** in solution (Scheme 2, Table 1).

The reactions proceeded to completion in 2–3 h, and the pure products were obtained simply by recrystallization from methanol; no chromatographic purification was necessary. As

mentioned above, the enol forms exist only in solution and all compounds were obtained as keto forms from the reaction mixture. Notably, there is no signal for the OH group in Fourier-transform (FT)IR spectra because these spectra were recorded in the solid state. The keto/enol ratio was ~1 : 1 in all cases in chloroform, except with the strongly electron withdrawing nitro substituent in **1o**, where none of the enol tautomer could be detected. However, when the *N*-alkyl group was changed from methyl to ethyl, as in **1e**, the general 1 : 1 keto/enol ratio in solution was restored. The novel compounds listed in Table 1 were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, and elemental analyses.

As shown in Table 1, all the obtained pyranopyrimidine derivatives exist as mixtures of keto and enol tautomers in solution. In the ^{1}H NMR spectra of the products, the OH group of the enol tautomer shows a broad singlet at δ 8.21–13.18 ppm, and in keto tautomers, the α CH adjacent to the carbonyl of the aryloyl group shows a sharp singlet at δ 4.91–5.69 ppm, which was used to calculate the keto/enol ratio.

As suggested in Scheme 3, the formation of the product involves the initial regioselective formation of a Knoevenagel adduct **6** by condensation between **2** and **5**, followed by regioselective Michael addition between **6** and **5** to give the intermediate **7**, dehydration of which leads to the formation of products **1a**–**s**, and their enol tautomers **4a**–**s**.

As noted in our previous work, the initial attack of the 1,3-dialkyl-2-thiobarbituric acid occurred exclusively on the formyl group of the arylglyoxal and subsequent Michael addition also occurred regioselectively and chemoselectively.

The possible utility of the products described in the present paper is enhanced by noting that the high enol content of the products in solution allows their facile alkylation on carbon or oxygen, allowing modification of their shape or transport properties. This aspect of the work is being actively pursued.

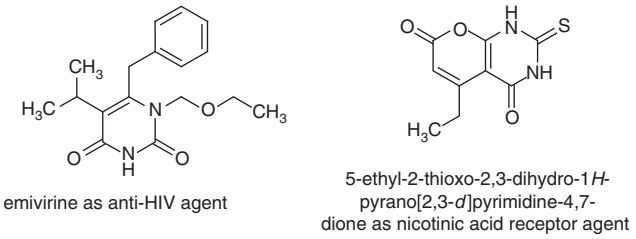
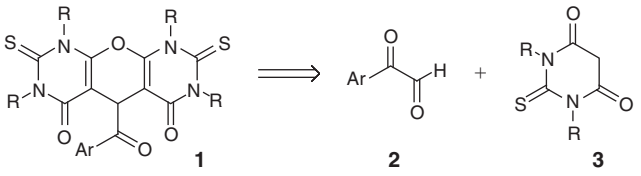


Fig. 1. Structure of two biologically active pyrimidine derivatives.



Scheme 1. Retrosynthesis of substituted 5-aryloyl-1*H*-pyrano[2,3-*d*] pyrimidine.

Conclusion

In summary, we have developed an efficient high-yielding protocol for the regio- and chemoselective synthesis of substituted symmetric pyrano[2,3-*d*]pyrimidines that does not require any catalyst. The protocol involves a two-component reaction of arylglyoxals with 1,3-dialkyl-2 thiobarbituric acids in ethanol at room temperature, leading to chemoselective synthesis of 5-aryloyl-1,3,7,9-tetraalkyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-diones. The advantages offered by this strategy are: simple operation, mild reaction conditions, ease of product isolation, and good to excellent yields.

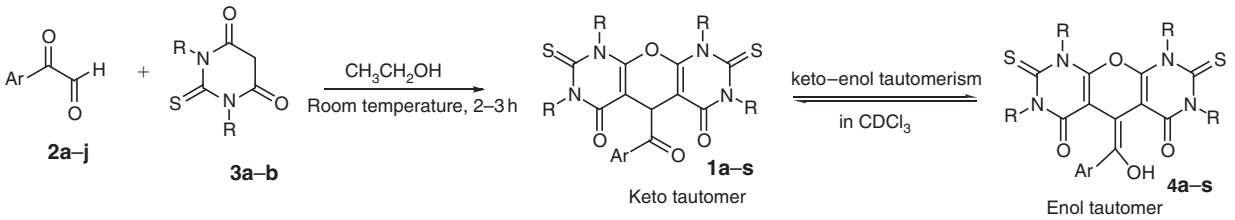
Experimental

General Procedures

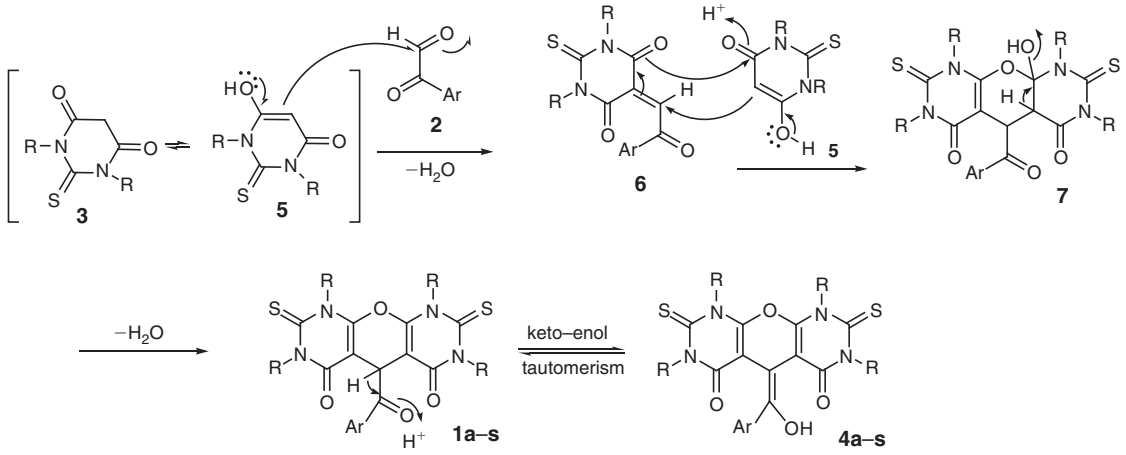
Arylglyoxals and 1,3-dimethyl-2-thiobarbituric acid were prepared by reported procedures.[33,34] Other starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to monitor the reactions were TLC and NMR. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were obtained on a Nexus-670 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were recorded on a Bruker DRX-300 Avance spectrometer at 300 and 75.5 MHz respectively. Elemental analyses were performed using a Leco Analyzer 932.

Table 1. Pyranopyrimidines prepared according to Scheme 2

Entry	Ar	R	Keto/enol ratio in $CDCl_3$ [%]
1a	C_6H_5	CH_3CH_2	52/48
1b	4-BrC_6H_4	CH_3CH_2	56/44
1c	4-ClC_6H_4	CH_3CH_2	40/60
1d	4-FC_6H_4	CH_3CH_2	45/55
1e	4-$NO_2C_6H_4$	CH_3CH_2	51/49
1f	4-$OCH_3C_6H_4$	CH_3CH_2	46/54
1g	3-BrC_6H_4	CH_3CH_2	52/48
1h	3-$OCH_3C_6H_4$	CH_3CH_2	51/49
1i	3,4-$(OCH_3)_2C_6H_3$	CH_3CH_2	33/67
1j	3,4-$(OCH_2O)C_6H_3$	CH_3CH_2	56/44
1k	C_6H_5	CH_3	49/51
1l	4-BrC_6H_4	CH_3	58/42
1m	4-ClC_6H_4	CH_3	35/65
1n	4-FC_6H_4	CH_3	47/53
1o	4-$NO_2C_6H_4$	CH_3	100/0
1p	4-$OCH_3C_6H_4$	CH_3	50/50
1q	3-BrC_6H_4	CH_3	51/49
1r	3-$OCH_3C_6H_4$	CH_3	52/48
1s	3,4-$(OCH_3)_2C_6H_3$	CH_3	44/56



Scheme 2. Synthesis of substituted pyranopyrimidine derivatives.



Scheme 3. Proposed mechanism for regio- and chemoselective formation of substituted pyrano[2,3-*d*]pyrimidines.

*General Procedure for the Synthesis of 5-Aryloyl-1,3,7,9-tetraalkyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-diones*

A mixture of 1,3-diethyl (or dimethyl)-2-thiobarbituric acid (1 mmol) and arylglyoxal (1 mmol) in absolute ethanol (10 mL) was stirred at room temperature for 2–3 h. After the appropriate time, the resulting precipitate was filtered and washed with ethanol. The crude products were recrystallized from methanol.

*5-Benzoyl-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1a***

Cream powder, 79 %, mp 197°C (dec.). δ_H 1.12 (t, *J* 6.9, 6H, 2 × CH_3), 1.36 (t, *J* 6.9, 6H, 2 × CH_3), 4.49 (q, *J* 6.9, 4H, 2 × CH_2), 4.62 (q, *J* 6.9, 4H, 2 × CH_2), 5.57 (s, 1H, CH in keto tautomer), 7.37 (t, *J* 7.5, 2H, Ar), 7.49 (t, *J* 7.5, 1H, Ar), 7.67 (d, *J* 7.5, 2H, Ar), 10.06 (bs, 1H, OH in enol tautomer). δ_C 11.6, 12.0, 41.5, 44.5, 44.9, 95.9, 127.6, 128.2, 132.7, 136.0, 162.3, 162.9, 174.5, 194.4. ν_{max} (KBr)/cm^{-1} 2981, 2935, 2520, 1694, 1622, 1444, 1384, 1269, 1110, 785. Anal. Calc. for $C_{24}H_{26}N_4O_4S_2$: C 57.81, H 5.26, N 11.24, S 12.86. Found: C 57.90, H 5.29, N 11.30, S 12.90 %.

*5-(4-Bromobenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1b***

Pink powder, 81 %, mp 193°C (dec.). δ_H 1.15 (t, *J* 6.9, 6H, 2 × CH_3), 1.35 (t, *J* 6.9, 6H, 2 × CH_3), 4.50 (q, *J* 6.3, 4H, 2 × CH_2), 4.61 (q, *J* 6.3, 4H, 2 × CH_2), 5.52 (s, 1H, CH in keto tautomer), 7.57–7.48 (m, 4H, Ar), 11.58 (bs, 1H, OH in enol tautomer). δ_C 11.6, 12.0, 41.4, 44.6, 45.0, 95.6, 127.7, 129.1, 131.5, 134.8, 162.4, 162.9, 174.4, 193.4. ν_{max} (KBr)/cm^{-1} 2981, 2934, 2521, 1700, 1621, 1585, 1437, 1383, 1269, 1110, 798. Anal. Calc. for $C_{24}H_{25}BrN_4O_4S_2$: C 49.91, H 4.36, N 9.70, S 11.10. Found: C 49.84, H 3.31, N 9.88, S 11.14 %.

*5-(4-Chlorobenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1c***

Yellow powder, 85 %, mp 202°C (dec.). δ_H 1.16 (t, *J* 6.3, 6H, 2 × CH_3), 1.33 (t, *J* 6.3, 6H, 2 × CH_3), 4.51 (q, *J* 6.3, 4H, 2 × CH_2), 4.62 (q, *J* 6.3, 4H, 2 × CH_2), 5.53 (s, 1H, CH in keto tautomer), 7.36 (d, *J* 8.4, 2H, Ar), 7.63 (d, *J* 8.1, 2H, Ar), 9.47 (bs, 1H, OH in enol tautomer). δ_C 11.6, 12.0, 41.4, 44.6, 45.0, 95.7, 128.6, 129.0, 134.3, 139.1, 162.4, 162.9, 174.4, 193.2. ν_{max} (KBr)/cm^{-1} 2982, 2935, 2875, 2516, 1699, 1621, 1435. Anal. Calc. for $C_{24}H_{25}ClN_4O_4S_2$: C 54.08, H 4.73, N 10.51, S 12.03. Found: C 54.12, H 4.70, N 10.60, S 12.10 %.

*5-(4-Fluorobenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1d***

Pink powder, 80 %, mp 204°C (dec.). δ_H 1.15 (bt, *J* 6.9, 6H, 2 × CH_3), 1.35 (bt, *J* 6.3, 6H, 2 × CH_3), 4.50 (q, *J* 6.3, 4H, 2 × CH_2), 4.62 (q, *J* 6.3, 4H, 2 × CH_2), 5.54 (s, 1H, CH in keto tautomer), 7.08–7.02 (m, 2H, Ar), 7.73–7.69 (m, 2H, Ar), 9.78 (bs, 1H, OH in enol tautomer). δ_C 11.6, 12.0, 41.4, 44.6, 45.0, 95.8, 115.3, 115.6, 130.2, 130.3, 132.2, 162.4, 162.9, 163.5, 166.9, 174.4, 192.8. ν_{max} (KBr)/cm^{-1} 3075, 2984, 2520, 1698, 1623, 1597, 1440, 1383, 1269, 1110, 849, 783. Anal. Calc. for $C_{24}H_{25}FN_4O_4S_2$: C 55.80, H 4.88, N 10.85, S 12.41. Found: C 55.78, H 4.89, N 10.96, S 12.50 %.

*5-(4-Nitrobenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1e***

Grey powder, 88 %, mp 223°C (dec.). δ_H 1.15 (t, *J* 6.6, 6H, 2 × CH_3), 1.36 (t, *J* 6.6, 6H, 2 × CH_3), 4.49 (q, *J* 6.6, 4H, 2 × CH_2), 4.62 (q, *J* 6.6, 4H, 2 × CH_2), 5.58 (s, 1H, CH in keto tautomer), 7.76 (d, *J* 8.7, 2H, Ar in enol tautomer), 7.84 (d, *J* 8.7, 2H, Ar in keto tautomer), 8.25 (d, *J* 8.7, 2H, Ar in keto tautomer), 8.28 (d, *J* 8.7, 2H, Ar in enol tautomer), 9.92 (bs, 1H, OH in enol tautomer). δ_C 11.6, 11.9, 41.8, 44.6, 44.9, 95.1, 123.4, 125,6, 128.6, 141.4, 149.8, 161.5, 162.3, 163.0, 174.4, 193.2. ν_{max} (KBr)/cm^{-1} 3078, 2976, 2934, 2521, 1709, 1619, 1528, 1430, 1382, 1271, 1110, 857, 798. Anal. Calc. for $C_{24}H_{25}N_5O_6S_2$: C 53.03, H 4.64, N 12.88, S 11.80. Found: C 53.00, H 4.68, N 13.01, S 11.83 %.

*5-(4-Methoxybenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1f***

Pink powder, 82 %, mp 202°C (dec.). δ_H 1.52–1.02 (m, 12H, 4 × CH_3), 3.84 (s, 3H, OCH_3), 4.77–4.27 (m, 8H, 4 × CH_2), 5.55 (s, 1H, CH in keto tautomer), 6.85 (d, *J* 8.7, 2H, Ar), 7.69 (d, *J* 8.7, 2H, Ar), 9.44 (bs, 1H, OH in enol tautomer). δ_C 11.6,

12.0, 41.5, 44.5, 45.0, 55.4, 96.0, 112.5, 119.3, 119.9, 129.1, 137.2, 159.4, 162.4, 162.8, 174.4, 194.1. ν_{max} (KBr)/cm^{-1} 2981, 2935, 2521, 1688, 1620, 1437, 1383, 1263, 1109, 780. Anal. Calc. for $C_{25}H_{28}N_4O_5S_2$: C 56.80, H 5.34, N 10.60, S 12.13. Found: C 56.84, H 5.36, N 10.69, S 12.18 %.

*5-(3-Bromobenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′] dipyrimidine-4,6(5*H*,7*H*)-dione* ***1g***

Pink powder, 75 %, mp 179°C (dec.). δ_H 1.18 (t, *J* 6.9, 6H, 2 × CH_3), 1.37 (t, *J* 6.9, 6H, 2 × CH_3), 3.91 (q, *J* 6.9, 4H, 2 × CH_2), 3.94 (q, *J* 6.9, 4H, 2 × CH_2), 5.59 (s, 1H, CH in keto tautomer), 7.03 (d, *J* 6.9, 1H, Ar), 7.32–7.25 (m, 3H, Ar), 11.63 (bs, 1H, OH in enol tautomer). δ_C 11.6, 12.0, 41.6, 44.6, 45.0, 95.6, 122.4, 125.9, 129.7, 130.9, 135.5, 137.8, 162.3, 162.9, 174.5, 193.0. ν_{max} (KBr)/cm^{-1} 2955, 2878, 2559, 1708, 1633, 1592, 1459, 1375, 1110, 878, 795. Anal. Calc. for $C_{24}H_{25}BrN_4O_4S_2$: C 49.91, H 4.36, N 9.70, S 11.10. Found: C 49.93, H 4.37, N 9.81, S 11.17 %.

*5-(3-Methoxybenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′] dipyrimidine-4,6(5*H*,7*H*)-dione* ***1h***

White powder, 77 %, mp 179°C (dec.). δ_H 1.15 (t, *J* 6.3, 6H, 2 × CH_3), 1.35 (t, *J* 6.3, 6H, 2 × CH_3), 3.81 (s, 3H, OCH_3), 4.51 (q, *J* 6.3, 4H, 2 × CH_2), 4.61 (q, *J* 6.3, 4H, 2 × CH_2), 5.56 (s, 1H, CH in keto tautomer), 7.04 (d, *J* 7.8, 1H, Ar in enol tautomer), 7.30–7.18 (m, 3H, Ar), 10.95 (bs, 1H, OH in enol tautomer). δ_C 11.6, 12.0, 41.5, 44.6, 45.0, 55.4, 96.0, 112.5, 119.3, 119.9, 129.1, 137.2, 159.4, 162.4, 162.8, 174.5, 194.1. ν_{max} (KBr)/cm^{-1} 2979, 2934, 2523, 1702, 1621, 1445, 1380, 1269, 1110, 790. Anal. Calc. for $C_{25}H_{28}N_4O_5S_2$: C 56.80, H 5.34, N 10.60, S 12.13. Found: C 56.79, H 5.39, N 10.71, S 12.16 %.

*5-(3,4-Dimethoxybenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano [2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1i***

Grey powder, 84 %, mp 201°C (dec.). δ_H 1.47–0.90 (m, 12H, 4 × CH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.72–4.33 (m, 8H, 4 × CH_2), 5.57 (s, 1H, CH in keto tautomer), 6.77 (d, *J* 8.4, 1H, Ar in),7.26 (d, *J* 8.4, 1H, Ar in enol tautomer), 7.34 (s, 1H, Ar), 12.01 (bs, 1H, OH in enol tautomer). δ_C 11.9, 41.4, 44.3, 44.7, 55.9, 56.0, 96.3, 109.8, 110.8, 121.7, 128.4, 148.7, 153.0, 162.6, 174.4, 192.6. ν_{max} (KBr)/cm^{-1} 2987, 2898, 2542, 1692, 1623, 1561, 1472, 1385, 1270, 1112, 771. Anal. Calc. for $C_{26}H_{30}N_4O_6S_2$: C 55.90, H 5.41, N 10.03, S 11.48. Found: C 55.95, H 4.44, N 10.10, S 11.53 %.

*5-(3,4-Methylenedioxybenzoyl)-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano [2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1j***

Pink powder, 83 %, mp 161°C (dec.). δ_H ($CDCl_3$, 300 MHz) 1.23 (t, *J* 7.5, 6H, 2 × CH_3), 1.34 (t, *J* 7.5, 6H, 2 × CH_3), 4.71–4.29 (m, 8H, 4 × CH_2), 5.53 (s, 1H, CH in keto tautomer), 6.03 (s, 2H, CH_2), 6.76 (d, *J* 8.1, 1H, Ar in), 7.26–7.14 (m, 2H, Ar), 7.34 (s, 1H, Ar), 8.21 (bs, 1H, OH in enol tautomer). δ_C 11.8, 11.9, 44.7, 44.8, 96.1, 101.8, 123.4, 130.1, 147.8, 151.5, 163.1, 174.5, 192.4. ν_{max} (KBr)/cm^{-1} 2982, 2935, 2527, 1701, 1620, 1440, 1383, 1269, 1250, 1110, 1038, 793, 731. Anal. Calc. for $C_{25}H_{26}N_4O_6S_2$: C 55.34, H 4.83, N 10.33, S 11.82. Found: C 55.31, H 4.81, N 10.45, S 11.88 %.

*5-Benzoyl-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′] dipyrimidine-4,6(5*H*,7*H*)-dione* ***1k***

Cream powder, 83 %, mp 202°C (dec.) δ_H ($CDCl_3$, 300 MHz) 3.84–3.58 (m, 12H, 4 × CH_3), 5.69 (s, 1H, CH in keto tautomer), 7.40 (t, *J* 7.5, 2H, Ar), 7.53 (t, *J* 7.5, 1H, Ar), 7.73 (d, *J* 7.5, 2H, Ar), 8.55 (bs, 1H, OH in enol tautomer). δ_C 35.3, 36.6, 41.5, 95.9, 127.8, 128.5, 133.0, 135.7, 162.8, 163.2, 175.4, 194.2. ν_{max} (KBr)/cm^{-1} 2952, 2869, 2484, 1702, 1621, 1467, 1394, 1339, 1295, 1339, 1110, 789. Anal. Calc. for $C_{24}H_{26}N_4O_4S_2$: C 57.81, H 5.26, N 11.24, S 12.86. Found: C 57.90, H 5.29, N 11.30, S 12.90 %.

*5-(4-Bromobenzoyl)-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′] dipyrimidine-4,6(5*H*,7*H*)-dione* ***1l***

Pink powder, 87 %, mp 237°C (dec.). δ_H 3.62 (s, 6H, 2 × CH_3), 3.84 (s, 6H, 2 × CH_3), 5.63 (s, 1H, CH in keto tautomer), 7.55 (d, *J* 8.4, 2H, Ar), 7.61 (d, *J* 8.1, 2H, Ar), 9.49 (bs, 1H, OH in enol tautomer). δ_C 36.4, 36.6, 41.5, 95.7, 128.1, 129.3, 131.9, 134.5, 162.7, 163.2, 175.4, 193.2. ν_{max} (KBr)/cm^{-1} 2947, 2556, 1706, 1619, 1586, 1461, 1391, 1342, 1111, 810. Anal. Calc. for $C_{20}H_{17}BrN_4O_4S_2$: C 46.07, H 3.29, N 10.75, S 12.30. Found: C 46.10, H 3.31, N 10.66, S 12.35 %.

*5-(4-Chlorobenzoyl)-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′] dipyrimidine-4,6(5*H*,7*H*)-dione* ***1m***

Yellow powder, 86 %, mp 227°C (dec.). δ_H 3.71 (s, 6H, 2 × CH_3), 3.82 (s, 6H, 2 × CH_3), 5.63 (s, 1H, CH in keto tautomer), 7.46 (d, *J* 6.9, 2H, Ar), 7.67 (d, *J* 6.9, 2H, Ar), 8.58 (bs, 1H, OH in enol tautomer). δ_C 36.9, 37.1, 41.7, 96.3, 128.7, 129.8, 132.8, 135.1, 161.6, 163.1, 177.3, 192.8. ν_{max} (KBr)/cm^{-1} 2951, 2932, 2551, 1708, 1620, 1590, 1465, 1387, 1226, 1110, 790. Anal. Calc. for $C_{20}H_{17}ClN_4O_4S_2$: C 50.36, H 3.59, N 11.75, S 13.45. Found: C 50.32, H 3.57, N 11.60, S 13.50 %.

*5-(4-Fluorobenzoyl)-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′] dipyrimidine-4,6(5*H*,7*H*)-dione* ***1n***

Pink powder, 84 %, mp 210°C (dec.). δ_H 3.72 (s, 6H, 2 × CH_3), 3.83 (s, 6H, 2 × CH_3), 5.65 (s, 1H, CH in keto tautomer), 7.11–7.05 (m, 2H, Ar), 7.79–7.75 (m, 2H, Ar), 11.21 (bs, 1H, OH in enol tautomer). δ_C 36.6, 41.5, 95.8, 115.6, 115.9, 130.4, 130.5, 131.9, 132.0, 162.7, 163.1, 163.7, 167.1, 175.4, 192.6. ν_{max} (KBr)/cm^{-1} 3069, 2981, 2538, 1692, 1618, 1588, 1472, 1381, 1264, 856, 778. Anal. Calc. for $C_{20}H_{17}FN_4O_4S_2$: C 52.16, H 3.72, N 12.17, S 13.93. Found: C 52.14, H 3.75, N 12.01, S 13.97 %.

*5-(4-Nitrobenzoyl)-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′] dipyrimidine-4,6(5*H*,7*H*)-dione* ***1o***

Beige powder, 92 %, mp 228°C (dec.). δ_H 3.70 (s, 6H, 2 × CH_3), 3.85 (s, 6H, 2 × CH_3), 5.69 (s, 1H, CH in keto tautomer), 7.89 (d, *J* 8.7, 2H, Ar in keto tautomer), 8.27 (d, *J* 8.7, 2H, Ar in keto tautomer). δ_C 36.4, 36.7, 42.0, 95.1, 123.7, 124.6, 128.7, 141.0, 150.1, 162.7, 175.4, 202.5. ν_{max} (KBr)/cm^{-1} 2951, 2541, 1713, 1621, 1526, 1394, 1345, 1109, 789. Anal. Calc. for $C_{20}H_{17}N_5O_6S_2$: C 49.27, H 3.51, N 14.37, S 13.15. Found: C 49.30, H 3.55, N 14.30, S 13.19 %.

*5-(4-Methoxybenzoyl)-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1p***

Pink powder, 87 %, mp 201°C (dec.). δ_H 3.14 (s, 6H, 2 × CH_3), 3.16 (s, 6H, 2 × CH_3), 3.83 (s, 3H, OCH_3), 4.91 (s, 1H, CH of keto tautomer), 6.87 (d, *J* 8.4Hz, 2H, Ar), 7.32 (d, *J* 8.1Hz, 2H, Ar), 9.49 (s, 1H, OH in enol tautomer). δ_C 36.6, 41.3, 55.4, 96.1, 113.8, 114.2, 128.1, 130.2, 131.0, 162.8, 163.5, 175.4, 192.8. ν_{max} (KBr)/cm^{-1} 2947, 2560, 1691, 1595, 1466, 1395, 1338, 1171, 1110, 1023, 787. Anal. Calc. for $C_{21}H_{20}N_4O_5S_2$: C 53.38, H 4.27, N 11.86, S 13.57. Found: C 53.41, H 4.25, N 11.77, S 13.61 %.

*5-(3-Bromobenzoyl)-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1q***

Pink powder, 79 %, mp 152°C (dec.). δ_H 3.72 (s, 6H, 2 × CH_3), 3.82 (s, 6H, 2 × CH_3), 5.67 (s, 1H, CH in keto tautomer), 7.06 (d, *J* 5.4, 1H, Ar), 7.32–7.25 (m, 3H, Ar), 13.18 (bs, 1H, OH in enol tautomer). δ_C 36.7, 41.6, 96.0, 112.8, 119.5, 119.9, 129.7, 136.9, 159.6, 162.7, 175.4, 193.9. ν_{max} (KBr)/cm^{-1} 2941, 2548, 1700, 1625, 1579, 1470, 1365, 1111, 875, 790. Anal. Calc. for $C_{20}H_{17}BrN_4O_4S_2$: C 46.07, H 3.29, N 10.75, S 12.30. Found: C 46.12, H 3.32, N 10.68, S 12.39 %.

*5-(3-Methoxybenzoyl)-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1r***

Pink powder, 80 %, mp 187°C (dec.). δ_H 3.72 (s, 3H, OCH_3), 3.83 (s, 12H, 2 × CH_3), 5.68 (s, 1H, CH in keto tautomer), 7.32–7.26 (m, 3H, Ar), 7.70 (d, *J* 7.5, 1H, Ar), 9.38 (bs, 1H, OH in enol tautomer). δ_C 36.5, 41.6, 55.3, 96.0, 112.7, 119.5, 119.9, 129.4, 136.9, 159.6, 163.0, 175.4, 193.9. ν_{max} (KBr)/cm^{-1} 2946, 2557, 1697, 1607, 1455, 1340, 1168, 1110, 1025, 752. Anal. Calc. for $C_{21}H_{20}N_4O_5S_2$: C 53.38, H 4.27, N 11.86, S 13.57. Found: C 53.37, H 4.24, N 11.83, S 13.60 %.

*5-(3,4-Dimethoxybenzoyl)-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1*H*-pyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(5*H*,7*H*)-dione* ***1s***

Grey powder, 82 %, mp 207°C (dec.). δ_H 3.67 (s, 6H, 2 × CH_3), 3.79 (s, 6H, 2 × CH_3), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.70 (s, 1H, CH in keto tautomer), 6.80 (d, *J* 8.4, 1H, Ar), 7.30 (d, *J* 8.7, 1H, Ar), 7.44 (s, 1H, Ar), 8.90 (bs, 1H, OH in enol tautomer). δ_C 36.6, 41.2, 55.9, 56.0, 96.3, 110.9, 121.9, 128.1, 149.0, 153.3, 162.8, 175.4, 192.7. ν_{max} (KBr)/cm^{-1} 3001, 2932, 2874, 2834, 2529, 1696, 1618, 1516, 1465, 1338, 1265, 1111, 1026, 790. Anal. Calc. for $C_{22}H_{22}N_4O_6S_2$: C 52.58, H 4.41, N 11.15, S 12.76. Found: C 52.55, H 4.40, N 11.10, S 12.85 %.

Supplementary Material

IR, ^{1}H NMR and ^{13}C NMR spectra of pyranopyrimidine derivatives are available on the Journal's website.

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