Efficient access to novel 5-aryloyl-1*H*-pyrano[2,3-*d*:6,5-*d'*]-dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetraones and their sulfur analogs in water

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Abstract

An efficient chemoselective synthesis of novel substituted pyrano[2,3-*d*]pyrimidines is described. A number of pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetraones and their sulfur analogs were synthesized through a one-pot condensation of arylglyoxal monohydrates with barbituric acid and thiobarbituric acid in the presence of excess ammonium acetate in water at room temperature, affording the desired products in moderate to good yields.

Keywords: Pyranopyrimidine, arylglyoxalmonohydrate, barbituric acid, thiobarbituric acid, chemoselective

Introduction

The synthesis of complex organic molecules needs to rely on methods that provide maximum efficiency in modern research in organic chemistry. Combinatorial chemistry has emerged as a powerful synthetic procedure in this area. Obtaining scaffolds from the combination of multiple transformations in a single-pot designated as domino reactions, is a highly efficient means for improvement of the reaction efficiency.[1] Also, Combinatorial chemistry is being increasingly applied for the discovery of novel biologically active compounds. In this context, multicomponent reactions (MCRs) are a powerful tool in the modern drug discovery process in terms of lead finding and lead optimization.[2,3]

In recent years, special attention has been focused on the use of water as a green solvent in various organic transformations. In addition to its abundance and for economical and safety reasons, water has naturally become a substitute and an alternative environmentally benign solvent in organic synthesis.[4,5] The use of aqueous medium as solvent further reduces the

harmful effects of organic solvents on the environment. The growing environmental awareness in chemical research and pharmaceutical chemistry, due to their traditionally large volume of waste/product ratios, is perhaps the ripest area for greening. Green chemistry approaches have considerable potential not only for the reduction of byproducts, decreasing waste produced and lowering energy costs, but also for the development of new methodologies for the previously inaccessible materials, using existing technologies.[6]

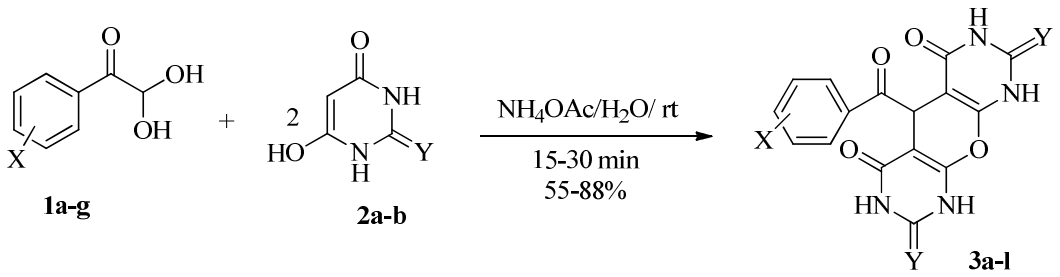
Pyran derivatives are of considerable interest as they possess a wide range of biological properties such as spasmolytic, diuretic, antiallergic, anticoagulant, anticancer, and antianaphylactic activity, etc.[7-9] Polyfuctionalized pyran derivatives are common structural subunits in variety of important natural products.[8-11] In addition, they can be used as cognitive enhancers, for the treatment of neurodegenerative diseases.[12] A number of 2-amino-2*H*-pyrans are useful as photoactive substances also.[13] There are some methods reported in the literature for the synthesis of polyfuctionalized pyran derivatives.[14,15] Unfortunately, many of these processes suffer from limitations such as long reaction times, hazardous by-products, microwave irradiations, use of stoichiometric, or even excess amount of base, and use of metal triflates.[16-18]

Therefore, the development of cleaner technologies is a major emphasis in green chemistry. Among the several aspects of green chemistry, the reduction/replacement of volatile organic solvents from the reaction medium and instead the using of water as the safest solvent in organic synthesis is of utmost importance. We have recently interested in one-pot synthesis of various heterocyclic systems.[19,20] In view of the importance of green syntheses of pyran derivatives, we report herein a novel green approach for efficient synthesis of new substituted pyranopyrimidine derivatives. In this communications, some 1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetraones and their sulfur analogs bearing various aryloyl substituents at 5 position of the ring were synthesized from the reaction of arylglyoxalmonohydrates and barbituric acid or thiobarbituric acid in the presence of excess ammonium acetate in water at room temperature.

Results and Discussion

Following to our recent work on the synthesis of new substituted pyranopyrimidines,[20] we found that unlike 1,3-diethyl and 1,3-dimethylthiobarbituric acids, stirring the mixture of barbituric acid or thiobarbituric acid and arylglyoxalmonohydrates in ethanol in both room temperature and reflux conditions in order to synthesis of the corresponding 5-aryloyl substituted pyrano[2,3-*d*]pyrimidines was failed which this phenomenon may be because of poor solublity of barbituric acid and thiobarbituric acid in ethanol. Therefore, we changed the reaction solvent to water as a suitable solvent for barbituric acid derivatives. Stirring arylglyoxalmonohydrates and barbituric acid or thiobarbituric acid in water in both room temperature and reflux conditions led to form a clear solution and there were no precipitations in reaction vessels. Randomly, we stirred the mixture of arylglyoxalmonohydrates **1a-g** and barbituic acid **2a** or thiobarbituric acid **2b** in the

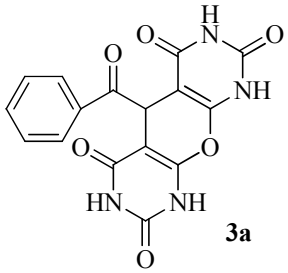
presence of excess ammonium acetate in water at room temperature which led to form significant precipitates. These precipitates were isolated and recrystallized in methanol. Our aim from adding ammonium acetate to the reaction mixture was the synthesis of pyrrolopyrimidine derivatives but considering ^{1}H-nmr spectra of all products showed that similar to our previously synthesized dialkyl substituted pyrano[2,3-*d*]pyrimidines,[20] there is a singlet in the average chemical shift 5.5 ppm which relates to CH of pyran ring. Namely, ammonium acetate instead of addition on carbonyl groups of 1,4-dicarbonyl intermediate acts as catalyst in these reactions and it helps to close pyran system on the pyrimidinone rings. Also, in ^{13}C-NMR spectrum of the most of compounds, the CH of pyran ring which is adjacent to carbonyl of aryloyl group resonates in δ≈53.0 ppm. The synthesis of these new pyranopyrimidines was shown in Scheme 1.



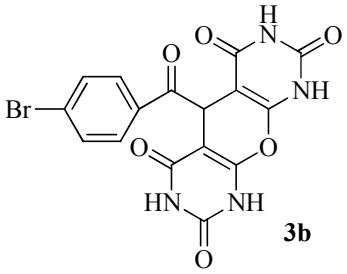
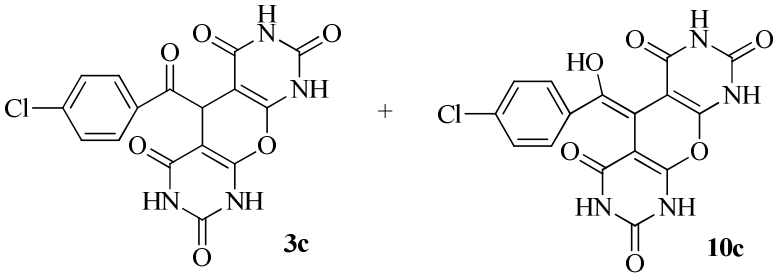
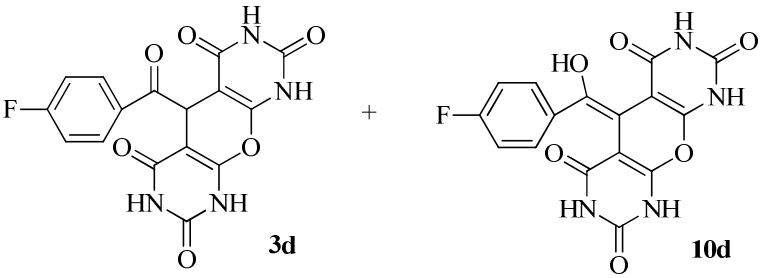
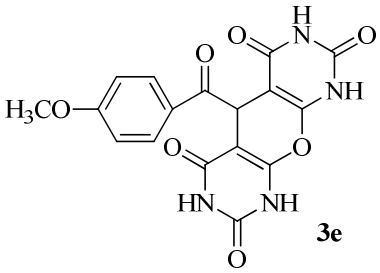
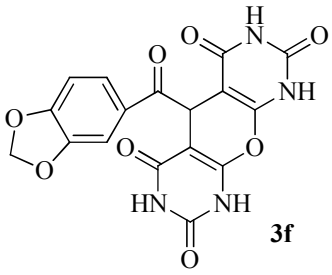
Scheme 1. Synthesis of 5-aryloyl-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetraones and their sulfur analogs.

The structure of all products **3a-l** are listed in Table 1.

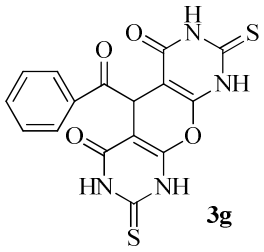
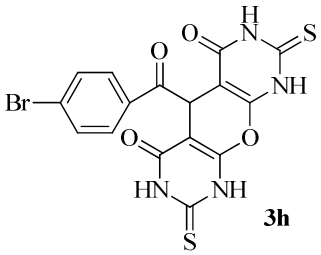
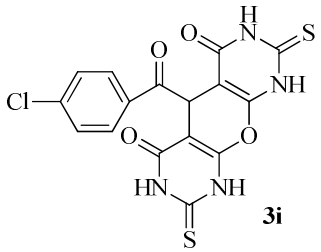
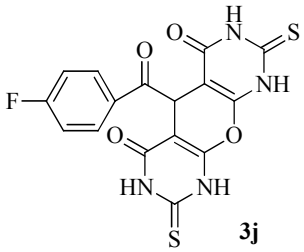
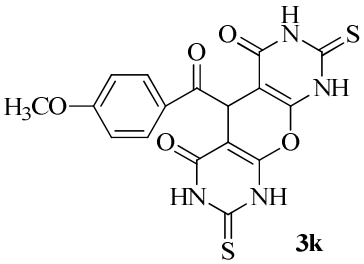
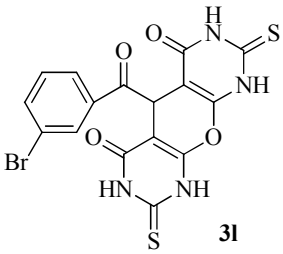
Table 1. List of 5-aryloyl-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetraones and their sulfur analogs

Entry	Substituted pyranopyrimidine	Yield (%)
1	 **3a**	70

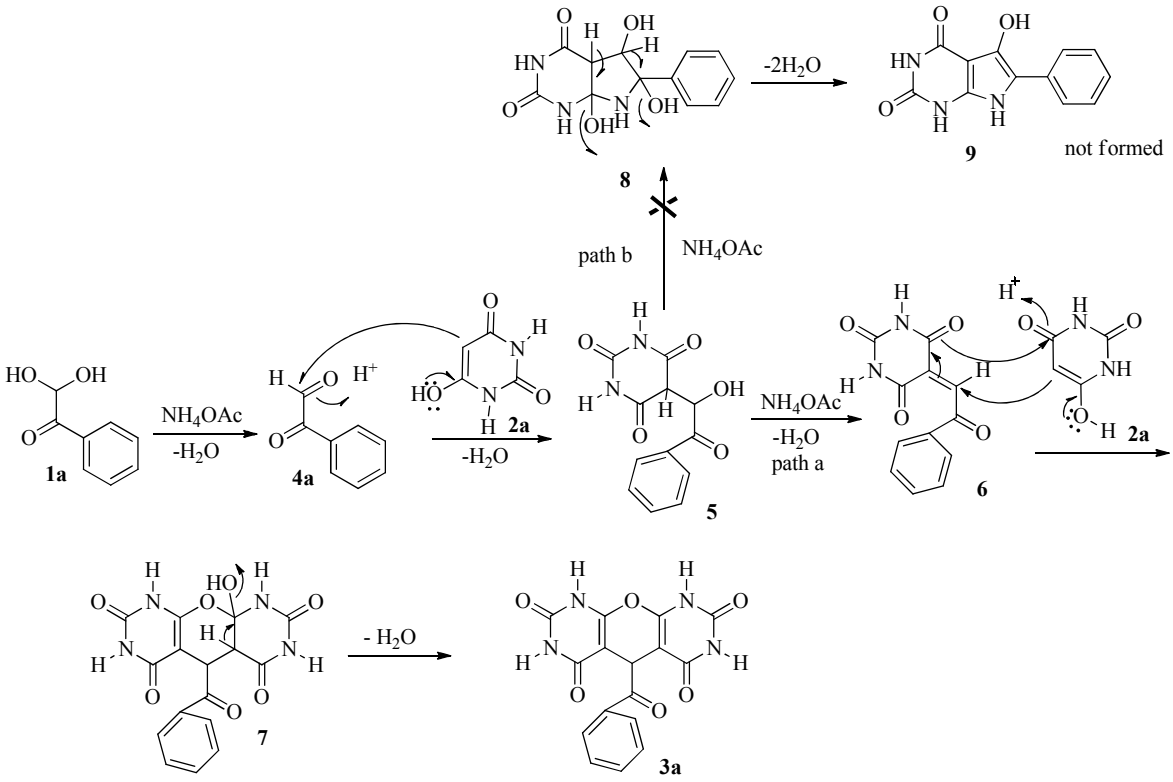
Tabel 1 (continued)

2	 **3b**	62
3	 **3c** + **10c**	74
4	 **3d** + **10d**	69
5	 **3e**	88
6	 **3f**	81

Tabel 1 (continued)

7	 **3g**	68
8	 **3h**	55
9	 **3i**	59
10	 **3j**	70
11	 **3k**	72
12	 **3l**	75

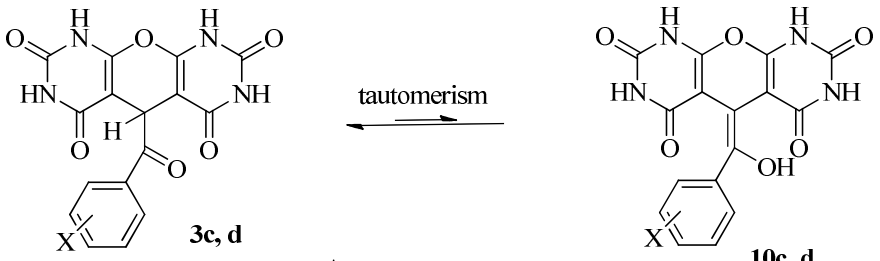
The suggested mechanism is schematized in Scheme **2** which fully accords with the obtained results.



Scheme 2. Plausible mechanism for chemoselective synthesis of 5-aryloyl substituted pyrano[2,3-*d*]pyrimidine derivatives**.**

As shown in the Scheme 2, the reaction was handeled by regioselective addition of barbituric acid **2a** on aldehyde carbonyl of phenylglyoxal **4a**, leading to 1,4-dicarbonyl intermediate **5**. In the presence of ammonium acetate, instead of addition of NH_3 (obtained from NH_4OAc) to the corresponding intermediate **5** in order to formation of the pyrrolopyrimidine **9**, only the dehydration reaction was done which led to form the intermediate **6**. This phenomenon is the reflection of chemoselective behavior of this reaction. Subsequent Michael addition of barbituric acid **2a** on the *α*,*β*-unsaturated intermediate **6** led to form final pyranopyrimidine **3a** after one step dehydration reaction. Therefore, this synthetic strategy acts fully regio-chemoselective and there is no evidence for formation of other products.

The keto-enol tautomerism is occurred only in 4-Cl and 4-F derivatives in d_6-DMSO solution and the predominant tautomer in both derivatives was keto one (Scheme 3).



Entry	X	Keto : Enol (%)
1	4-Cl	58 : 42
2	4-F	56 : 44

Scheme 3. Keto-enol tautomerism in pyrano[2,3-*d*]pyrimidines.

Conclusions

We described a simple approach to efficient chemoselective one pot two component reaction of arylglyoxalmonohydrates and barbituric acid or thiobarbituric acid in the presence of ammonium acetate as an acidic catalyst in water to afford 5-aryloyl-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetraones and their sulfur analogs in good yields. Using water as the greenest solvent, applying ammonium acetate as a cheap catalyst, short reaction times, high yielding of the products, easy workup, chemoselectivity and regioselectivity are the advantages of this novel strategy.

Experimental Section

General. Arylglyoxalmonohydrates were prepared by reported procedure.[21] Other starting materials and solvents were purchased from Merck and Acros companies and were used without further purification. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were measured on a Perkin Elmer Spectrum Two spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz AVANCE spectrometer at 300 and 75 MHz, respectively. Elemental analyses were performed using a Leco Analyzer *932*.

General procedure for synthesis of 5-aryloyl-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetraones

A mixture of barbituric acid (2 mmol) and arylglyoxalmonohydrates (1 mmol) in the presence of excess ammonium acetate (5 mmol) was stirred at room temperature for 15-25 minutes which led to form the title compounds as white powders. The crude products were filtered and washed with

excess water (20 mL) then recrystallized from methanol to give pure compounds in 62-88% yields.

5-Benzoyl-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetraone (3a). white powder, 70%, mp 245 °C (dec.). ^{1}H-NMR (d_6-DMSO) δ (ppm) 9.39 (s, 2H, NH), 7.93 (d, *J* 7.2Hz, 2H, Ar), 7.74 (s, 2H, NH), 7.56 (t, *J* 7.5Hz, 1H, Ar), 7.43 (d, *J* 7.2Hz, 2H, Ar), 5.50 (s, 1H, CH). ^{13}C-NMR (d_6-DMSO) δ (ppm) 165.0, 164.1, 152.3, 134.7, 133.5, 128.7, 128.4, 128.2, 80.8, 53.4. FT-IR (KBr) ν_{max}/ cm^{-1}: 3420, 3134, 2040, 2853, 1693, 1581, 1471, 1388, 1320, 1235, 782, 754, 533. Anal. Calcd for $C_{16}H_{10}N_4O_6$, C 54.24, H 2.85, N 15.81; found C 54.20, H 2.91, N 15.70.

5-(4-Bromobenzoyl)-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8 (3*H*,5*H*,7*H*,9*H*)-tetraone (3b). White powder, 62%, mp 259 ºC (dec.). ^{1}H NMR (d_6-DMSO) δ 9.40 (s, 2H, NH), 7.83 (d, *J* 8.4 Hz, 2H, Ar), 7.73 (s, 2H, NH), 7.62 (d, *J* 8.7 Hz, 2H, Ar), 5.46 (s, 1H, CH). ^{13}C NMR (d_6-DMSO) δ 194.4, 164.4, 164.1, 152.3, 133.8, 131.8, 130.1, 127.5, 80.5, 53.5. FT-IR (KBr) ν_{max}/ cm^{-1}: 3184, 3056, 1690, 1641, 1615, 1584, 1448, 1387, 1268, 1089, 777, 538. Anal. Calcd for $C_{16}H_9BrN_4O_6$, C 44.36, H 2.09, N 12.93; found C 44.32, H 2.11, N 13.12

5-(4-Chlorobenzoyl)-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8 (3*H*,5*H*,7*H*,9*H*)-tetraone (3c) and its enol tautomer (10c). white powder, 74%, mp 241 ºC (dec.). ^{1}H NMR (d_6-DMSO) δ 15.85 (bs, 1H, OH in enol tautomer), 10.03 (s, 2H, NH), 7.71 (d, *J* 7.50 Hz, 2H, Ar), 7.41 (d, *J* 8.4 Hz, 2H, Ar), 7.23 (s, 2H, NH), 6.03 (s, 1H, CH in keto tautomer). ^{13}C NMR (d_6-DMSO) δ 198.7, 164.8, 151.0, 136.7, 130.0, 129.6, 128.8, 128.3, 88.4, 38.4. FT-IR (KBr) ν_{max}/ cm^{-1}: 3372, 3237, 1685, 1610, 1400, 1343, 1257, 1175, 1092, 812, 776, 550. Anal. Calcd for $C_{16}H_9ClN_4O_6$, C 49.44, H 2.33, N 14.41; found C 49.49, H 2.30, N 14.32.

5-(4-Fluorobenzoyl)-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8 (3*H*,5*H*,7*H*,9*H*)-tetraone (3d) and its enol tautomer (10d). White powder, 69%, mp 220 ºC (dec.). ^{1}H NMR (d_6-DMSO) δ 15.84 (bs, 1H, OH in enol tautomer), 10.02 (s, 2H, NH), 7.8-7.76 (m, 2H, Ar), 7.23 (s, 2H, NH), 7.19-7.14 (m, 2H, Ar), 6.04 (s, 1H, CH in keto tautomer). ^{13}C NMR (d_6-DMSO) δ 198.2, 166.1, 164.8, 162.8, 151.0, 134.3, 134.3, 130.6, 130.4, 115.3, 115.0, 88.5, 38.3. FT-IR (KBr) ν_{max}/ cm^{-1}: 3422, 3112, 3044, 2899, 1696, 1655, 1566, 1508, 1459, 1371, 1233, 1162, 1097, 843, 798, 546. Anal. Calcd for $C_{16}H_9FN_4O_6$, C 51.62, H 2.44, N 15.05; found C 51.56, H 2.49, N 14.86.

5-(4-Methoxybenzoyl)-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8 (3*H*,5*H*,7*H*,9*H*)-tetraone (3e). White powder, 88%, mp 239 ºC (dec.). ^{1}H NMR (d_6-DMSO) δ 9.41 (s, 2H, NH) 7.95 (d, *J* 9Hz, 2H, Ar), 7.77 (s, 2H, NH), 6.95 (d, *J* 7.8 Hz, 2H, Ar), 5.44 (s, 1H, CH), 3.76 (s, 3H, OCH3). ^{13}C NMR (d_6-DMSO) δ 193.4, 164.4, 164.1, 163.5, 152.3, 130.6, 127.3, 114.0, 81.0, 55.9, 53.3. FT-IR (KBr) ν_{max}/ cm^{-1}: 3331, 3160, 2835, 1707, 1670, 1650, 1609, 1573, 1461, 1396, 1320, 1267, 1178, 1020, 804, 777. Anal. Calcd for $C_{17}H_{12}N_4O_7$, C 53.13, H 3.15, N 14.58, found C 53.16, H 3.14, N 14.50.

5-(3,4-Methylenedioxybenzoyl)-1*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(3*H*,5*H*,7*H*,-9*H*)-tetraone (3f). White powder, 81%, mp 227 ºC (dec.). ^{1}H NMR (d_6-DMSO) δ 9.40 (s, 2H, NH), 7.76 (s, 2H, NH), 7.61 (dd, J_1 8.4Hz, J_2 1.8Hz, 1H, Ar), 7.48 (d, *J* 1.5 Hz, 1H, Ar), 6.95 (d,

J 8.1 Hz, 1H, Ar), 6.09 (s, 2H, CH_2), 5.40 (s, 1H, CH). ^{13}C NMR (d_6-DMSO) δ 192.9, 164.4, 164.1, 152.3, 151.9, 147.7, 128.8, 124.5, 108.3, 108.1, 102.3, 80.7, 53.3. FT-IR (KBr) ν_{max}/ cm^{-1}: 3338, 3176, 1705, 1670, 1604, 1504, 1455, 1377, 1318, 1268, 1098, 1040, 777. Anal. Calcd for $C_{17}H_{10}N_4O_8$, C 51.27, H 2.53, N 14.07; found C 51.30, H 2.60, N 13.90.

General procedure for synthesis of 5-aryloyl-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 thiobarbituric acid (2 mmol) and arylglyoxalmonohydrates (1mmol) in the presence of excess ammonium acetate (5mmol) was stirred at room temperature for 20-30 minutes which led to form the title compounds as white powders. The crude products were filtered and washed with excess water (20 mL) then recrystallized from methanol to give pure compounds in 55-75% yields.

5-Benzoyl-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 (3g). White powder, 68%, mp 207 ºC (dec.), ^{1}H NMR (d_6-DMSO) δ 9.45 (s, 2H, NH), 7.93 (d, *J* 8.1Hz, 2H, Ar), 7.78 (bs, 2H, NH), 7.56 (t, *J* 7.5 Hz, 1H, Ar), 7.42 (t, *J* 7.5 Hz, 2H, Ar), 5.50 (s, 1H, CH). ^{13}C NMR (d_6-DMSO) δ 194.7, 164.0, 163.7, 151.9, 134.2, 133.1, 128.3, 128.0, 80.4, 53.0. FT-IR (KBr) ν_{max}/ cm^{-1}: 3198, 3009, 2891, 1704, 1653, 1636, 1600, 1445, 1292, 1271, 1207, 1140, 822, 748. Anal. Calcd for $C_{16}H_{10}N_4O_4S_2$, C 49.73, H 2.61, N 14.50, S 16.60; found C 49.80, H 2.67, N 14.31, S 16.68.

5-(4-Bromobenzoyl)-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 (3h). White powder, 55%, mp 231 ºC (dec.), ^{1}H NMR (d_6-DMSO) δ 11.67 (s, 2H, NH), 8.08 (bs, 2H, NH), 7.97 (d, *J* 8.4Hz, 2H, Ar), 7.71 (d, *J* 8.4Hz, 2H, Ar), 5.36 (s, 1H, CH). ^{13}C NMR (d_6-DMSO) δ 197.4, 173.1, 162.7, 135.8, 131.2, 129.3, 126.0, 118.9, 92.9, 53.0. FT-IR (KBr) ν_{max}/ cm^{-1}: 3283, 3060, 2887, 1695, 1628, 1586, 1560, 1447, 1292, 1271, 1139, 833, 798. Anal. Calcd for $C_{16}H_9BrN_4O_4S_2$, C 41.30, H 1.95, N 12.04, S 13.78; found C 41.35, H 2.03, N 11.90, S 13.84.

5-(4-Chlorobenzoyl)-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 (3i). White powder, 59%, mp 248 ºC (dec.), ^{1}H NMR (d_6-DMSO) δ 11.63 (s, 2H, NH), 7.68 (d, *J* 8.4Hz, 2H, Ar), 7.44 (d, *J* 8.4Hz, 2H, Ar), 6.04 (s, 1H, CH), 5.08 (bs, 2H, NH). ^{13}C NMR (d_6-DMSO) δ 197.2, 175.0, 162.7, 137.0, 135.5, 129.2, 128.3, 114.2, 92.9, 41.9. FT-IR (KBr) ν_{max}/ cm^{-1}: 3283, 2885, 1694, 1631, 1590, 1555, 1445, 1270, 1292, 1137, 1089, 832, 706. Anal. Calcd for $C_{16}H_9ClN_4O_4S_2$, C 45.66, H 2.16, N 13.31, S 15.24; found C 45.58, H 2.10, N 13.25, S 15.32.

5-(4-Fluorobenzoyl)-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 (3j). White powder, 70%, mp 215 ºC (dec.), ^{1}H NMR (d_6-DMSO) δ 9.49 (s, 2H, NH), 8.02-7.97 (m, 2H, Ar), 7.78 (bs, 2H, NH), 7.29-7.23 (m, 2H, Ar), 6.04 (s, 1H, CH). ^{13}C NMR (d_6-DMSO) δ 193.4, 166.7, 163.8, 152.0, 151.9, 131.0, 130.9, 130.8, 115.6, 115.3, 80.1, 53.0. FT-IR (KBr) ν_{max}/ cm^{-1}: 3289, 2884, 1702, 1631, 1592, 1560, 1520, 1466, 1346, 1209, 1137, 815. Anal. Calcd for $C_{16}H_9FN_4O_4S_2$, C 47.52, H 2.24, N 13.85, S 15.86; found C 47.61, H 2.29, N 13.74, S 15.96.

5-(4-Methoxybenzoyl)-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 (3k). White powder, 72%, mp 255 ºC (dec.). ^{1}H NMR (d_6-DMSO) δ 11.63 (s, 2H, NH), 7.69 (d, *J* 8.7Hz, 2H, Ar), 7.26 (bs, 2H, NH), 6.89 (d, *J* 8.7Hz, 2H, Ar), 6.02 (s, 1H, CH), 3.77 (s, 3H, OCH3). ^{13}C NMR (d_6-DMSO) δ 196.3, 173.0, 162.8, 162.4, 136.9, 133.2, 129.8, 129.2, 113.4, 93.5, 55.4. FT-IR (KBr) ν_{max}/ cm^{-1}: 3273, 3079, 2967, 1683, 1627, 1566, 1449, 1334, 1273, 1206, 1143, 785. Anal. Calcd for $C_{17}H_{12}N_4O_5S_2$, C 49.03, H 2.90, N 13.45, S 15.40; found C 49.00, H 2.95, N 13.23, S 15.48.

5-(3-Bromobenzoyl)-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 (3l). White powder, 75%, mp 221 ºC (dec.), ^{1}H NMR (d_6-DMSO) δ 9.52 (s, 2H, NH), 8.03 (s, H, Ar), 7.87 (d, *J* 7.8Hz, 1H, Ar), 7.75 (d, *J* 8.1Hz, 1H, Ar), 7.65 (bs, 2H, NH), 7.40 (t, *J* 7.8Hz, 1H, Ar), 5.50 (s, 1H, CH). ^{13}C NMR (d_6-DMSO) δ 193.7, 169.8, 163.7, 151.9, 136.4, 135.7, 130.5, 130.4, 126.6, 121.6, 80.2, 53.1. FT-IR (KBr) ν_{max}/ cm^{-1}: 3281, 2935, 2851, 1693, 1567, 1514, 1402, 1237, 1101, 883, 781. Anal. Calcd for $C_{16}H_9BrN_4O_4S_2$, C 41.30, H 1.95, N 12.04, S 13.78; found C 41.37, H 1.99, N 12.21, S 13.89.

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