One-pot Synthesis of Novel 2,8-dithioxopyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1*H*)-dione Catalyzed by *p*-Toluenesulfonic Acid

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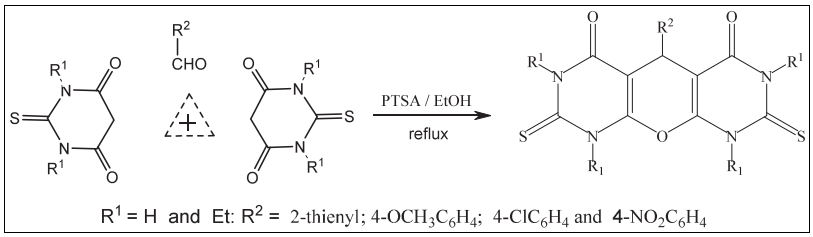
Received September 11, 2013
DOI 10.1002/jhet.2165
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



Novel 2,8-dithioxopyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1*H*)-dione derivatives were synthesized by a clean and efficient methodologies involving one-pot regioselective and chemoselective reactions between two moles substituted thiobarbituric acid and 1 mol various aromatic aldehydes in the presence of *p*-toluenesulfonic acid as a catalyst in EtOH with good yields in compression with alternative conditions such as microwave and promoted ultrasound. All of the compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data, and elemental analyses.

J. Heterocyclic Chem., **00,** 00 (2016).

INTRODUCTION

Over the past years, the preparation of pyranopyrimidines is of large interest in view of the pharmacological activities associated with this system such as cardiotonic [1], antibronchitic [2], antihypertensive [3], and antitumor [4,5] activity. It can be assumed that pyranopyrimidines have dual biological properties of both the pyran and the pyrimidine rings. This is reported that pyran derivatives exhibit growth stimulating effects [6], hypotensive effect [7], antifungal and plant growth regulation effects [8], central nervous system activity [9], antimicrobial activity [10], antitumor activity [11], and as antiproliferation agents [12,13]. On the other hand, pyrimidine has great biological and medicinal [14] applications including antiviral [15], antihypertensive [16], antibacterial [17], and antitumor activity [18].

The synthetic procedure of highly functional heterocyclic rings has been extensively investigated [19,20]. Despite the widespread developments in the synthesis of modified pyrimidines, little consideration has been paid about the chemistry of pyranopyrimidine [21]. The common procedures for the synthesis of pyrano[2,3-d]pyrimidines usually contain the reaction of benzylidenemalononitriles with barbituric acids in the presence of base catalysts [22,23]. For example, it has been reported that pyrano[2,3-d]pyrimidines synthesized subsequently *via* Knoevenagel, Micheal, and heterocyclization reactions of aldehyde, malononitrile, and barbituric acid/dimedone [24]. However, Prajapati and Gohain reported the formation of pyrano[2,3-d]pyrimidines and furopyrano[2,3-d]pyrimidines upon treating 1,3-dimethyl barbituric acid with an aromatic aldehyde and ethyl vinyl ether/2,3-dihydrofuran *via* a multicomponent Knoevenagel/hetero-Diels-Alder reactions in the presence of indium(III) chloride [25].

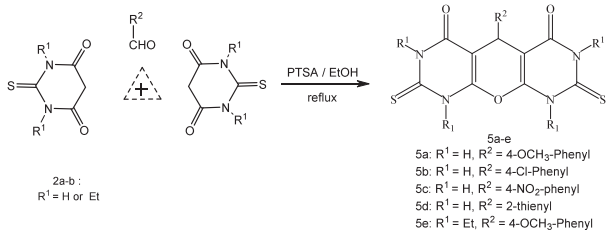
The more complex model of their preparation from malononitrile, aldehydes, and *N*,*N*′-dialkyl barbiturates is also well-known, and synthesis of pyrano[2,3-d]pyrimidine system is notable. However, as far as we look, multicomponent coupling reactions (MCRs) methodology especially based on the thiobarbituric acid was not still extended. In organic synthesis, MCRs have involved much consideration [26]. In other words, MCRs constitute particularly smart strategy in which several different starting materials react to a target product in a one-pot process. In addition, they are very useful tools in the current drug discovery procedure and allow the quick, automatic, and high-power achievement to organic complex constructions from simple precursors by formation of various novel bonds in one pot [27].

Here in contribution to our previous synthetic efforts [28–35], we describe one-pot three components synthesis of 5-substituted-2,8-dithioxo-2,3,5,7,8,9-hexahydro-4*H*-pyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1*H*)-dione derivatives *via* reaction of various aldehydes and thiobarbituric acid derivatives in the presence of *p*-toluenesulfonic acid (*p*-TSA) as catalyst in EtOH under reflux condition. Recently, the application of microwaves and ultrasound in synthesis is very popular because they frequently proceed greatly faster and carry products in higher yield and ultrapurity.

RESULTS AND DISCUSSION

In this protocol, we explain an efficient one-pot method for the regioselective synthesis of new pyranodipyrimidines

Scheme 1. Reaction of synthesized 2,8-dithioxopyrano[2,3-d:6,5-d′] dipyrimidine-4,6(1*H*)-dione derivatives **5a–e**.



5a–e *via* reaction of thiobarbituric acid as "active methylene" groups **2a–b** with different aromatic aldehydes **1a–d** under refluxing in EtOH containing *p*-TSA (Scheme 1).

The results are summarized in Table 1. The reaction is compared with other conditions such as catalyst, solvents, MW, and ultrasound.

The synthesis of **5a** was considered as representative example to determine the amount of *p*-TSA and effectiveness of this catalyst comparative to the other ones (Table 2).

Table 1

3-CR of synthesized 2,8-dithioxopyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1*H*)-dione derivatives.

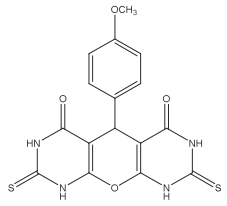
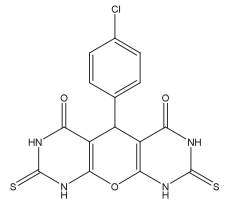
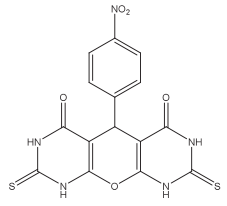
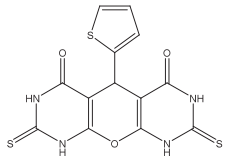
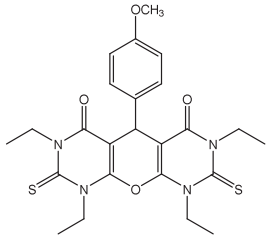
Entry	Structure of product	Melting point (°C)	Color	Reaction time (min)	Yield (%)
5a		320>	Orange	300	81
5b		305–307	Yellow	260	77
5c		315>	Deep yellow	320	72
5d		315>	Orange	310	79
5e		320>	Yellow	330	78

Table 2

Catalytic activity for the synthesis of pyranodipyrimidine **5a**.

Entry	Catalyst	Yield (%)	Time (min)
1	(0.2 mmol) *p*-TSA	68	330
2	(0.3 mmol) *p*-TSA	81	300
3	(0.4 mmol) *p*-TSA	77	300
4	H_2SO_4 (0.3 mmol)	59	500
5	H_2SO_4/SiO_2 (0.3 mmol)	65	380
6	$FeCl_3$ (0.3 mmol)	60	390
7	$FeCl_3$/KSF (0.3 mmol)	70	360

p-TSA, *p*-toluenesulfonic acid; KSF, Kilo-pound per square foot.

Table 2 demonstrates the amount of *p*-TSA in terms of time and yields of product and suggests it as an efficient catalyst relative to the other catalysts. Increasing the amount of *p*-TSA from 0.2 to 0.3 mmol decreased the reaction time from 330 to 300 min. In addition, the yield of the product also increased from 68% to 81% (entry 2, Table 2).

The choice of an appropriate reaction media is of critical importance for successful synthesis. Initially, the one-pot reaction of 2-mmol thiobarbituric acid **2a**, and 1-mmol benzaldehyde **1a** as a simple model substrate, was investigated to ascertain the possibility of the strategy and optimize the reaction conditions (Table 3). Different solvents in the presence of *p*-TSA as an inexpensive and available catalyst and various Lewis acids were screened in the model reaction. In the presence of *p*-TSA, the desired product **5a** that was obtained in good yield EtOH was the solvent of choice entry 4, Table 3. Synthesis of **5a** base on the reaction time and yield of the products under microwave and ultrasound conditions entries 4 and 5 indicates significant improvement (Table 3).

The structures of the synthesized compounds were established by FTIR, ^{1}H NMR, ^{13}C NMR, and elemental analyses. The IR spectrum of pyranodipyrimidines **5a–d** exhibited the characteristic band at 3100–3450 cm^{-1}, which indicates the presence of NH groups. The IR spectra of pyranodipyrimidines **5a–e** revealed the presence of absorption bands at $\upsilon = 1600–1650\ cm^{-1}$ because of C═O, absorption bands in the regions 1509–1610 cm^{-1} corresponding to aromatic ring, and peaks in the regions 1355–1365 and 1055–1096 cm^{-1}, which indicate the presence of C═S and C—N groups.

Table 3

Solvent effect for synthesis of pyranodipyrimidines **5a**.

Entry	Condition/solvent	Yield (%)	Time (min)	T (°C)
1	Reflux/CH_3CN	45	380	**85**
2	Reflux/DMF	45	480	**155**
3	Reflux/H_2O	Trace	600	**100**
4	Reflux/EtOH	81	300	**80**
5	MW	84	12	—
6	Ultrasound	83	30	**30**

Bold values signifies the solvent of choice is EtOH.

The structure of the compounds was further confirmed by ^{1}H NMR and ^{13}C NMR in DMSO-d_6. The ^{1}H NMR spectrum of pyranodipyrimidines **5a–d** exhibited two signals at δ 9–11.5 ppm because of the NH protones. The ^{1}H NMR spectrum of pyranodipyrimidines **5a–e** showed a sharp singlet at δ 5–6 (in **5c** appears in 8.6 ppm) because of CH benzylic protons. Protons belonging to the aromatic ring and substituted groups were observed within the expected chemical shift regions along with their integral values.

The ^{13}C NMR spectra of pyranodipyrimidines **5a–e** showed signals at 153.2–159.2 ppm assigned to carbonyl of the pyrimidine ring. Thiocarboxamide carbons (C═S) displayed a signal at 170.0–179.1 ppm for all of the compounds. The signals due to the aromatic and other substituted groups resonate at their usual positions (Experimental section).

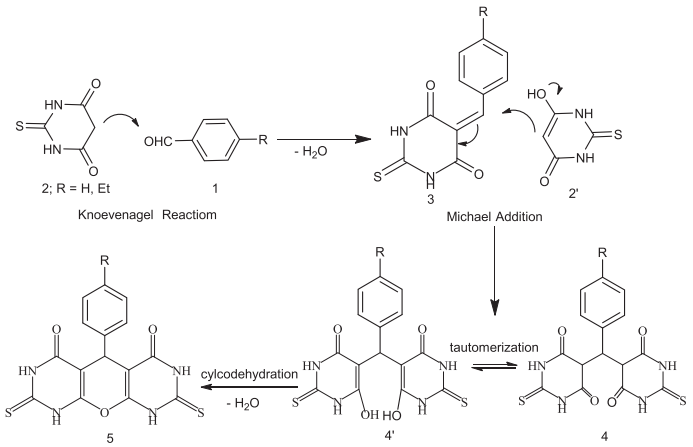
Investigation in the mechanism shows that reaction may continue at first *via* a Knoevenagel condensation of aldehyde **1** with thiobarbituric acid **2** to afford the Michael acceptor **3**. The active methylenes of thiobarbituric acids **2′** reacted then *via* its enol form with **3** to give the intermediate **4** tautomerized with **4′**. Intramolecular cyclizative condensation of **4** or **4′** afforded the expected products **5**. The products precipitated from the reaction mixture as pure solids and were easily recrystallized (Scheme 2).

In conclusion, this one-pot protocol provides regioselective and chemoselective, fast, and practical method for the preparation of novel pyranodipyrimidines from a variety of thiobarbituric acid and aldehyde derivatives in good yields. The best catalyst and solvent were *p*-TSA and EtOH. Under microwave and ultrasound conditions, significant improvements on the reaction time and yield of products were observed. The simplicity, high atom economy, easy execution, simple workup, and good yields, together with the use of inexpensive starting materials and an environmentally friendly process, are features of this procedure.

EXPERIMENTAL

The IR absorption band maxima were measured with a Shimadzu UV-2100 spectrophotometer (Shimadzu Corporation, Japan). Chemicals were purchased from Fluka, Merck, and Aldrich. Melting points are uncorrected and determined by Mettler Fp5 melting point apparatus. All NMR data were recorded in DMSO using a BrukerAvance 400-MHz spectrometer (Billerica, MA). Chemical shifts are reported in ppm (δ) using deuterated solvents as internal references. Elemental analyses were made by a Carlo-Erba EA1110 CHNO-S analyzer and agreed with the calculated values. For the microwave irradiation, a microwave oven equipped with a turntable was used (LG Smart Chef MS-255R operating at 2450 MHz having maximum output of 800 W) for reaction. For the ultrasound reactions, ultrasound apparatus Astra 3D (4.25 L, 37 kHz frequency, with heating power 200 W; Germany) from Elmasonic was used.

Scheme 2. Proposed mechanism for pyranodipyrimidines synthesis.



2,8-dithioxopyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1H)-dione (5a–e) (typical procedure). A mixture of thiobarbituric acid (0.14 g, 1 mmol), 4-methoxybenzaldehyde (0.65 g, 0.5 mmol) and *p*-TSA (0.05 g, 0.3 mmol) in refluxing EtOH (5 mL) was stirred for 5 h. Completion of the reaction confirmed by TLC (eluent: EtOAc/n-hexane, 1:3), the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water (10 mL) and EtOH (5 mL) to afford the pure **5a** as a yellow to orange powder.

5-(4-Methoxyphenyl)-2,8-dithioxo-2,3,5,7,8,9-hexahydro-4H-pyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1H)-dione (5a). Orange solid; Yield 81%; Mp > 320 °C; IR (KBr) (ν max/cm^{-1}): 3410, 3120, 1753, 1603, 1467, 1389, 1257, 1149, 882, 773, 670. ^{1}H NMR (400 MHz, DMSO): 12.31 (s, 2H, NH), 12.4(s, 2H, NH), 6.74–7.90 (d, 4H, J = 6.8 Hz, Ar-H), 5.95 (s, 1H, benzyl H), 3.86 (s, 3H, substituted-OCH_3(. ^{13}C NMR (100 MHz, DMSO) (δ/ppm): 178.25 (C═S), 163.95 (C═O), 114.30–139.73 (Ar-C), 93.14 (C of benzyl), 55.37 (substituted-OCH_3). Molecular weight: 388.42. *Anal. Calcd.* for $C_{16}H_{12}N_4O_4S_2$: C, 49.48; H, 3.11; N, 14.42. Found: C, 49.46; H, 3.07; N, 14.44.

5-(4-Chlorophenyl)-2,8-dithioxo-2,3,5,7,8,9-hexahydro-4H-pyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1H)-dione (5b). Yellow solid; Yield 77%; Mp 305–307 °C; IR (KBr) (ν max/cm^{-1}): 3410, 3120, 1753, 1603, 1467, 1389, 1257, 11368, 1149, 882, 773, 670. ^{1}H NMR (400 MHz, DMSO): 12.31 (s, 2H, NH), 12.4(S, 2H, NH), 6.74–7.90 (d, 4H, J = 8.8 Hz, Ar-H), 5.95 (s, 1H, benzyl H).^{13}C NMR (100 MHz, DMSO) (δ/ppm): 178.25 (C═S), 163.95 (C═O), 114.30–139.73 (Ar-C), 93.14 (C of benzyl). Molecular weight: 392.83. *Anal. Calcd.* for $C_{15}H_9ClN_4O_3S_2$: C, 45.86; H, 2.31; N, 14.26. Found: C, 45.85; H, 2.32; N, 14.25.

5-(4-Nitrophenyl)-2,8-dithioxo-2,3,5,7,8,9-hexahydro-4H-pyrano [2,3-d:6,5-d′]dipyrimidine-4,6(1H)-dione (5c). Deep yellow solid; Yield 72%; Mp > 315 °C; IR (KBr) (ν max/cm^{-1}): 3410, 3120, 1753, 1603, 1467, 1389, 1257, 11368, 1149, 882, 773, 670. ^{1}H NMR (400 MHz, DMSO): 11.74 (s, 4H, NH), 6.74–7.90 (d, 4H,J = 8.8 Hz, Ar-H), 6.04 (s, 1H, benzyl H(. ^{13}C NMR (100 MHz, DMSO) (δ/ppm): 178.25 (C═S), 163.95 (C═O), 114.30–139.73 (Ar-C), 93.14 (C of benzyl). Molecular weight: 403.39. *Anal. Calcd.* for $C_{15}H_9N_5O_5S_2$: C, 44.66; H, 2.25; N, 17.36. Found: C, 44.86; H, 2.24; N, 17.37.

5-(Thiophen-2-yl)-2,8-dithioxo-2,3,5,7,8,9-hexahydro-4H-pyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1H)-dione (5d). Orange solid; Yield 79%; Mp > 315 °C; IR (KBr) (ν max/cm^{-1}): 3410, 3120, 1753, 1603, 1467, 1389, 1257, 11368, 1149, 882, 773, 670.^{1}H NMR (400 MHz, DMSO): 12.41–12.38 (s, 4H, NH), 7.39–8.38 (d, 3H, J = 5.2 Hz, Ar-H), 8.60 (s, 1H, benzyl H).^{13}C NMR (100 MHz, DMSO) (δ/ppm): 178.31 (C═S), 161.74 (C═O), 128.70–160.83 (Ar-C), 111.30 (C of benzyl(. Molecular weight: 364.41. *Anal. Calcd.* for $C_{13}H_8N_4O_3S_3$: C, 42.85; H, 2.21; N, 15.37. Found: C, 42.86; H, 2.22; N, 15.36.

1,3,7,9-Tetraethyl-5-(4-methoxyphenyl)-2,8-dithioxo-2,3,5,7,8,9-hexahydro-4H-pyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1H)-dione (5e). Yellow solid; Yield 78%; Mp > 320 °C; IR (KBr) (ν max/cm^{-1}): 3410, 3120, 1753, 1603, 1467, 1389, 1257, 11368, 1149, 882, 773, 670.H. ^{1}HNMR (400 MHz, DMSO): 6.74–7.90 (d, 4H, Ar-H), 6.21 (s, 1H, benzyl H), 3.88 (s, 3H, substituted-OCH_3), 4.35 (m, 8H, NCH_2), 1.18 (m, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO) (δ/ppm): 172.89 (C═S), 162.92 (C═O), 121.30–141.73 (Ar-C), 95.49 (C of benzyl), 55.99 (substituted-OCH_3), 30.18 (CH_2), 18.52 (CH_3). Molecular weight: 500.63. *Anal. Calcd.* for $C_{24}H_{28}N_4O_4S_2$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.55; H, 5.65; N, 11.18.

Acknowledgment. Financial support from the Research Committee of University of Guilan is gratefully appreciated.

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