

## A green chemoselective one-pot protocol for expeditious synthesis of symmetric pyranodipyrimidine derivatives using $ZrOCl_2 \cdot 8H_2O$

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### ABSTRACT

A convenient, highly efficient and time economic method has been described for the chemo- and regioselective 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 derivatives by one-pot two-component reaction of 1,3-diethyl-2-thiobarbituric acid or 1,3-dimethyl-2-thiobarbituric acid with substituted arylglyoxalmonohydrates using commercially available zirconium (IV) oxydichloride octahydrate ( $ZrOCl_2 \cdot 8H_2O$ ) as green Lewis acid catalyst. This method is associated with some attractive characteristics such as good selectivity, very short reaction time, high yield of products, cleaner reaction profile, no harmful by-product, cheap and environmental benign catalyst, simple experimental and work-up procedure. This procedure does not require solvent separation and purification steps such as column chromatography.

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## 1. Introduction

Synthesis of required products in selective and environmentally friendly way is an enduring challenge in chemical sciences. Thus in recent times “Green Chemistry” which give us the guidelines for safer and eco-friendly method of chemical synthesis has gained significant attention both from the academia and industries.<sup>1-6</sup> Multi-component reactions (MCRs) especially those performed in water or ethanol can help chemists to conform their methodology with the requirements of “Green Chemistry” as well as to extend libraries of heterocyclic scaffolds.<sup>7-15</sup> Creating of highly efficient, selective, eco-friendly, and reusable catalysts is an interesting target of synthetic organic chemistry in academy and industry.<sup>16-21</sup>

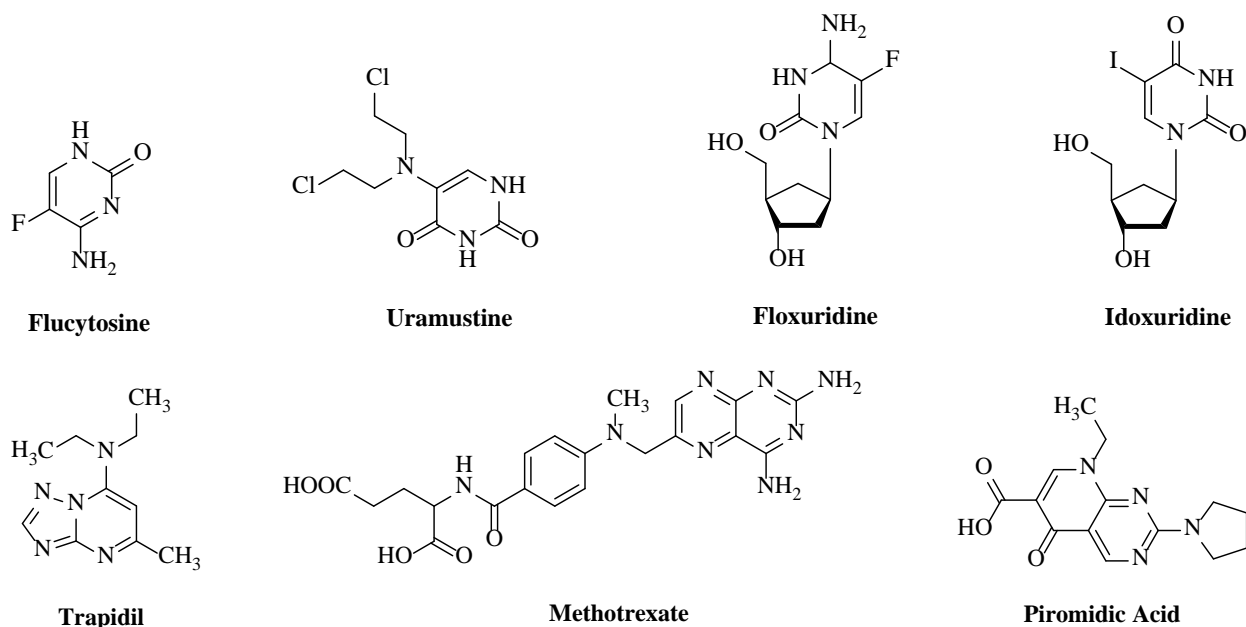
$ZrOCl_2 \cdot 8H_2O$  is a highly water-tolerant compound, which its handling does not need especial precautions.<sup>22-23</sup> Recently,  $ZrOCl_2 \cdot 8H_2O$  has emerged as very effective catalyst for various organic reactions such as Knoevenagel condensation,<sup>24</sup> Michael addition,<sup>25</sup> oxidation of alcohols,<sup>26</sup> acylation of alcohols, phenols, amines and thiols,<sup>27</sup> aerobic N-methylation of substituted Anilines,<sup>28</sup> esterification

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of long chain carboxylic acids,<sup>29</sup> one-pot synthesis of heterocyclic compounds,<sup>30-34</sup> and other organic transformations.

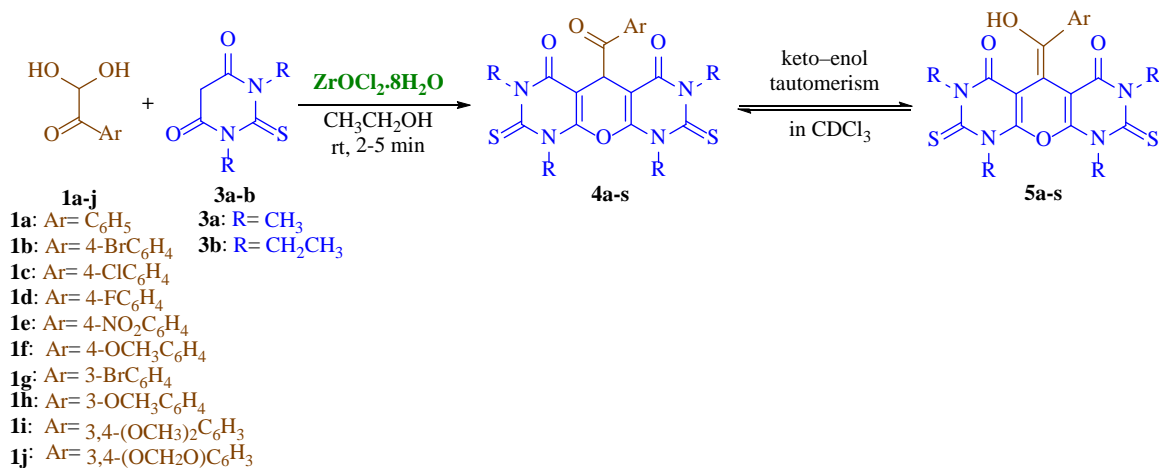
Pyrimidine derivatives and heterocyclic annulated pyrimidines display a wide spectrum of interesting pharmacological properties (**Fig. 1**).<sup>35-42</sup> The pyranopyrimidines showed a broad range of biological activities, such as antitubercular,<sup>43</sup> antimicrobial,<sup>44</sup> antiplatelet,<sup>45</sup> antifungal<sup>46</sup> and antitumor agents<sup>47</sup> as well as antiviral activities.<sup>48</sup> As a result, the development of efficient methods for the synthesis of these compounds is one of the most attractive fields in preparative chemistry.



**Fig. 1.** Examples of some substituted pyrimidine marketed drugs.

## 2. Results and Discussion

Because of the wide use of efficient and green Lewis acid catalyst in different areas of organic chemistry<sup>47-55</sup> and as part of our previous studies,<sup>56-62</sup> we report herein a highly efficient and expeditious method for the chemo- and regioselective 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*)-dione derivatives, via an one-pot two-component reaction of arylglyoxalmonohydrates (**1a-j**) and 1,3-dimethyl-2-thiobarbituric acid (**3a**) or 1,3-diethyl-2-thiobarbituric acid (**3b**). The syntheses were carried out in the presence of catalytic amount of  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  in ethanol at room temperature as shown on the Scheme 1.



**Scheme 1.**  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  catalyzed synthesis of pyrano[2,3-*d*:6,5-*d'*]dipyrimidine derivatives

Initially we have studied the reactions of phenylglyoxalmonohydrate (**1a**) with 1,3-dimethyl-2-thiobarbituric acid (**3a**) or 1,3-diethyl-2-thiobarbituric acid (**3b**) run in the presence of  $ZrOCl_2 \cdot 8H_2O$ , which was considered as green Lewis acid catalyst, in ethanol. Interestingly, the optimal catalyst loading in the synthesis of tetramethyl and tetraethyl substituted products was different. So that, in the synthesis of (**4a**) and (**4j**) were used 30 and 15 mol% of  $ZrOCl_2 \cdot 8H_2O$  respectively (Table 1, entry 6 and 13). When the reaction were carried out in water, target product was not formed even after 6 hours, in all conditions tested (room temperature, 50 °C and reflux) (Table 1, entry 7, 8, 9 and 16, 17, 18).

**Table 1.** Optimization of the reaction conditions

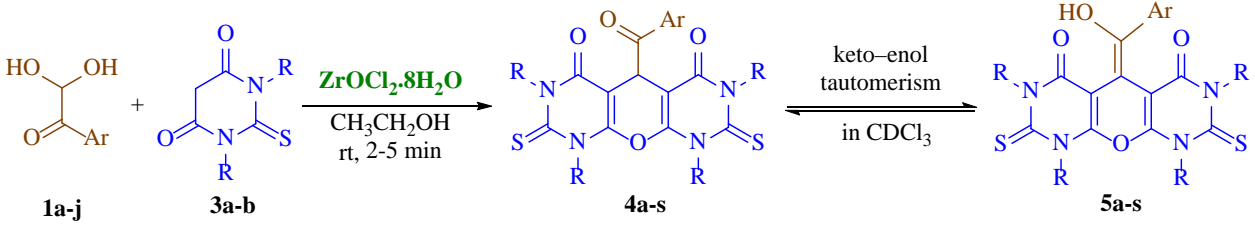
Entry	Solvent	R	Product	$ZrOCl_2 \cdot 8H_2O$ , mol%	Temp, °C	Time, min	Yield, %
1	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	-	r.t.	180 <sup>57</sup>	83
2	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	5	r.t.	60	75
3	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	10	r.t.	5	77
4	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	15	r.t.	3	82
5	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	20	r.t.	3	85
6	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	30	r.t.	3	91
7	H <sub>2</sub> O	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	20	r.t.	360	-
8	H <sub>2</sub> O	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	20	50	360	-
9	H <sub>2</sub> O	CH <sub>3</sub> ( <b>3a</b> )	<b>4a</b>	20	Reflux	360	-
10	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	-	r.t.	180 <sup>57</sup>	79
11	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	5	r.t.	5	89
12	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	10	r.t.	5	89
13	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	15	r.t.	3	95
14	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	20	r.t.	3	90
15	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	30	r.t.	3	90
16	H <sub>2</sub> O	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	20	r.t.	360	-
17	H <sub>2</sub> O	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	20	50	360	-
18	H <sub>2</sub> O	CH <sub>2</sub> CH <sub>3</sub> ( <b>3b</b> )	<b>4j</b>	20	Reflux	360	-

Next, we probed the generality and scope of the reaction. We were pleased to find that the reaction proceeded well with a different arylglyoxalmonohydrates (**1a-j**) and 1,3-dimethyl-2-thiobarbituric acid (**3a**) or 1,3-diethyl-2-thiobarbituric acid (**3b**) under optimized reaction conditions to give a library 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*)-dione derivatives (Table 1). The results of these reactions revealed that arylglyoxalmonohydrates bearing an electron-donating or electron-withdrawing group were well tolerated under the optimized conditions, with the corresponding pyrano[2,3-*d*:6,5-*d'*]dipyrimidine products (**4a-s**) being formed in excellent yields. However, the arylglyoxalmonohydrates with meta-position substituents offered lower yields than para-position substituents.

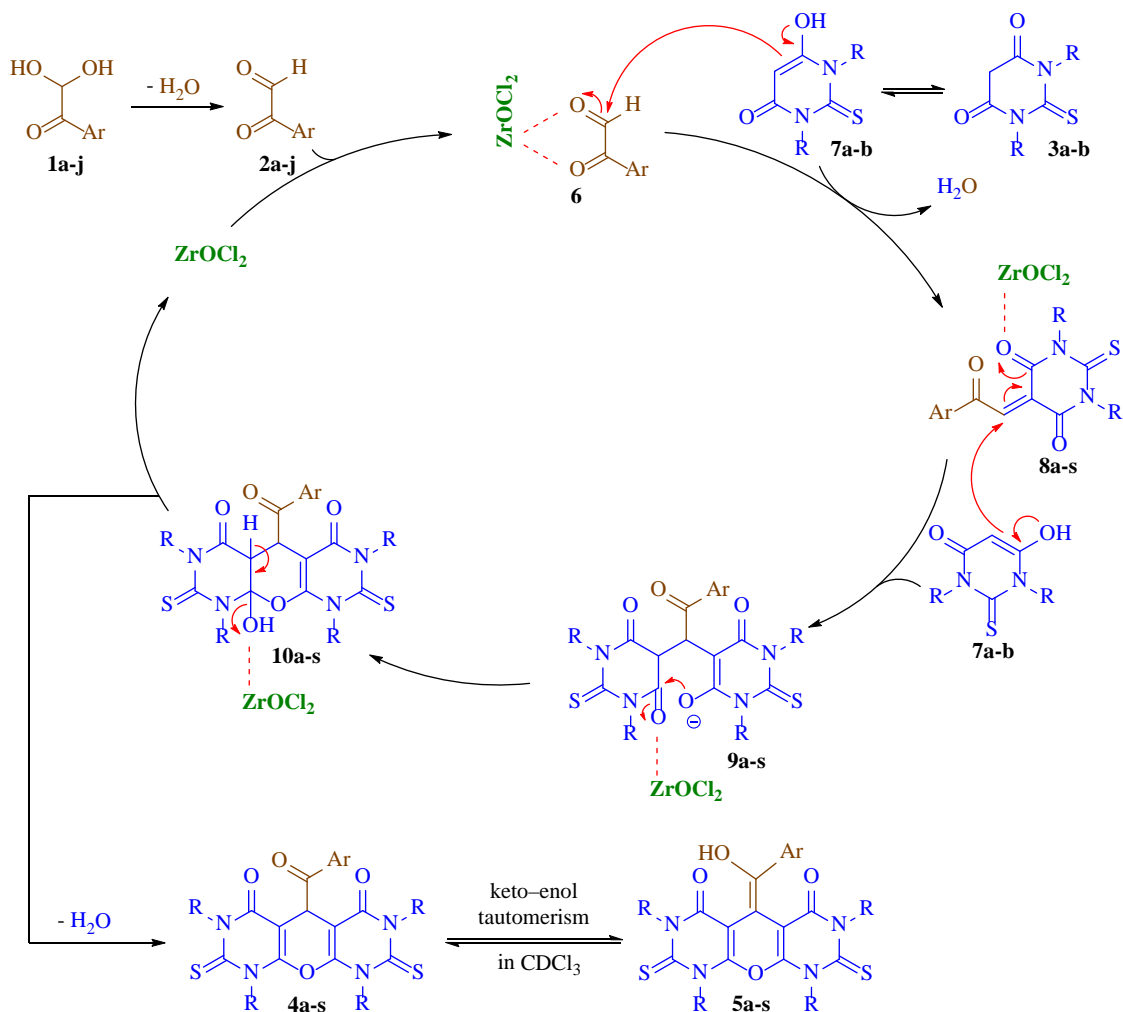
Finally, the structure of the all compounds were confirmed by means of IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectroscopies and by comparison with available data for previously reported pyrano[2,3-*d*:6,5-*d'*]dipyrimidines. In the CDCl<sub>3</sub> solution all pyrano[2,3-*d*:6,5-*d'*]dipyrimidine derivatives exist as mixture of keto and enol tautomers. In the <sup>1</sup>H-NMR spectra, the sharp singlet at 4.91-5.65 ppm, which belongs to CH of pyran ring, was present. Also broad singlet at 8.21-13.18 belongs to the OH group of the enol tautomer.

A proposed mechanism of the  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  catalyzed one-pot reaction for the rapid synthesis of **4a-s** is depicted on the Scheme 2. Based on literature<sup>22-34,63</sup> and own observations, we believed that the carbonyl groups of arylglyoxal (**2a-j**) is activated by  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  to give intermediate (**6**) which facilitates a regioselective nucleophilic attack of the enol form of (**3a-b**) followed by a dehydration reaction to give (**8a-s**). Then, Michael addition of (**7a-b**) to (**8a-s**) catalysed by  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  led to (**9a-s**). The cyclization of (**9a-s**) and dehydration of (**10a-s**) afforded the final products (**4a-s**).

**Table 2.** Chemoselective synthesis of pyrano[2,3-*d*:6,5-*d'*]dipyrimidine derivatives.



Entry	Arylglyoxal	R	Product	Time, min	Yield, %		Melting point, °C		Keto/enol ratio in $\text{CDCl}_3$ , %
					This work	Lit. <sup>57</sup>	Found	Lit. <sup>57</sup>	
1	<b>1a</b>	Me ( <b>3a</b> )	<b>4a</b>	3	95	83	201 (dec)	202 (dec)	49/51
2	<b>1b</b>	Me ( <b>3a</b> )	<b>4b</b>	2	96	87	238 (dec)	237 (dec)	58/42
3	<b>1c</b>	Me ( <b>3a</b> )	<b>4c</b>	2	96	86	225 (dec)	227 (dec)	35/65
4	<b>1d</b>	Me ( <b>3a</b> )	<b>4d</b>	2	95	84	211 (dec)	210 (dec)	47/53
5	<b>1e</b>	Me ( <b>3a</b> )	<b>4e</b>	2	99	92	228 (dec)	228 (dec)	100/0
6	<b>1f</b>	Me ( <b>3a</b> )	<b>4f</b>	3	96	87	200 (dec)	201 (dec)	50/50
7	<b>1g</b>	Me ( <b>3a</b> )	<b>4g</b>	5	90	79	154 (dec)	152 (dec)	51/49
8	<b>1h</b>	Me ( <b>3a</b> )	<b>4h</b>	5	94	80	188 (dec)	187 (dec)	52/48
9	<b>1i</b>	Me ( <b>3a</b> )	<b>4i</b>	4	95	82	210 (dec)	207 (dec)	44/56
10	<b>1a</b>	Et ( <b>3b</b> )	<b>4j</b>	2	91	79	199 (dec)	197 (dec)	52/48
11	<b>1b</b>	Et ( <b>3b</b> )	<b>4k</b>	3	96	81	197 (dec)	193 (dec)	56/44
12	<b>1c</b>	Et ( <b>3b</b> )	<b>4l</b>	2	97	85	201 (dec)	202 (dec)	40/60
13	<b>1d</b>	Et ( <b>3b</b> )	<b>4m</b>	2	96	80	205 (dec)	204 (dec)	45/55
14	<b>1e</b>	Et ( <b>3b</b> )	<b>4n</b>	2	98	88	222 (dec)	223 (dec)	51/49
15	<b>1f</b>	Et ( <b>3b</b> )	<b>4o</b>	2	96	82	203 (dec)	202 (dec)	46/54
16	<b>1g</b>	Et ( <b>3b</b> )	<b>4p</b>	3	92	75	180 (dec)	179 (dec)	52/48
17	<b>1h</b>	Et ( <b>3b</b> )	<b>4q</b>	4	93	77	177 (dec)	179 (dec)	51/49
18	<b>1i</b>	Et ( <b>3b</b> )	<b>4r</b>	4	97	84	203 (dec)	201 (dec)	33/69
19	<b>1j</b>	Et ( <b>3b</b> )	<b>4s</b>	2	97	83	165 (dec)	161 (dec)	56/44



**Scheme 2.** Proposed mechanism for the synthesis of symmetric pyranodipyrimidine derivatives catalyzed by  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$

### 3. Experimental

#### 3.1. General

Melting points were measured on an Electrothermal 9200 apparatus after the recrystallization of the products from methanol. IR spectra were recorded on a Nexus-670 FT-IR spectrometer in KBr.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300 and 75.5 MHz, respectively.

#### 3.2. General procedure for the preparation of 5-aryloyl-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1H-pyrano[2,3-d:6,5-d']dipyrimidine-4,6(5H,7H)-diones derivatives

A mixture of arylglyoxalmonohydrates (1 mmol) and 1,3-dimethyl-2-thiobarbituric acid (1 mmol) in the presence of  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  (30 mol%) in ethanol (5 mL) was stirred for 2-5 minutes at room temperature. Then, the resulting precipitate was filtered and washed with water (3×5 mL) and ethanol (2×5 mL). The crude products were purified by recrystallization from methanol. Selected spectral data is listed below.

*5-Benzoyl-1,3,7,9-tetramethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1H-pyrano[2,3-d:6,5-d']dipyrimidine-4,6(5H,7H)-dione (4a)* Cream powder,  $^1\text{H}$ NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.84–3.58 (m, 12H, 4× $\text{CH}_3$ ), 5.69 (s, 1H, CH in keto tautomer), 7.40 (t,  $J = 7.5$  Hz, 2H, Ar), 7.53 (t,  $J = 7.5$  Hz, 1H, Ar), 7.73 (d,  $J = 7.5$  Hz, 2H, Ar), 8.55 (br s, 1H, OH in enol tautomer) ppm.  $^{13}\text{C}$ NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$ : 35.3, 36.6,

41.5, 95.9, 127.8, 128.5, 133.0, 135.7, 162.8, 163.2, 175.4, 194.2 ppm. FT-IR (KBr)  $\nu_{\max}$ : 2952, 2869, 2484, 1702, 1621, 1467, 1394, 1339, 1295, 1339, 1110, 789  $\text{cm}^{-1}$ .

2.3. *General procedure for the preparation of 5-aryloyl-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1H-pyrano[2,3-d:6,5-d']dipyrimidine-4,6(5H,7H)-diones derivatives.*

A mixture of arylglyoxalmonohydrates (1 mmol) and 1,3-dimethyl-2-thiobarbituric acid (1 mmol) in the presence of  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  (15 mol%) in ethanol (5 mL) was stirred for 2-5 minutes at room temperature. Then, the resulting precipitates were filtered and washed with water (3×5 mL) and ethanol (2×5 mL). The crude products were purified by recrystallization from methanol. Selected spectral data is listed below.

5-Benzoyl-1,3,7,9-tetraethyl-2,8-dithioxo-2,3,8,9-tetrahydro-1H-pyrano[2,3-d:6,5-d']dipyrimidine-4,6(5H,7H)-dione (**4j**) Cream powder,  $^1\text{H}$ NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.12 (t,  $J = 6.9$ , 6H,  $2 \times \text{CH}_3$ ), 1.36 (t,  $J = 6.9$  Hz, 6H,  $2 \times \text{CH}_3$ ), 4.49 (q,  $J = 6.9$  Hz, 4H,  $2 \times \text{CH}_2$ ), 4.62 (q,  $J = 6.9$  Hz, 4H,  $2 \times \text{CH}_2$ ), 5.57 (s, 1H, CH in keto tautomer), 7.37 (t,  $J = 7.5$  Hz, 2H, Ar), 7.49 (t,  $J = 7.5$  Hz, 1H, Ar), 7.67 (d,  $J = 7.5$  Hz, 2H, Ar), 10.06 (br s, 1H, OH in enol tautomer) ppm.  $^{13}\text{C}$ NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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 ppm. IR (KBr)  $\nu_{\max}$ : 2981, 2935, 2520, 1694, 1622, 1444, 1384, 1269, 1110, 785  $\text{cm}^{-1}$ .

#### 4. Conclusions

In summary, we demonstrated a green, highly efficient and time-economic method for the synthesis of 5-aryloyl-1,3,7,9-tetraalkyl-2,8-dithioxo-2,3,8,9-tetrahydro-1H-pyrano[2,3-d:6,5-d']dipyrimidine-4,6(5H,7H)-dione derivatives. This reaction was achieved by using readily available arylglyoxalmonohydrates and 1,3-dialkyl-2-thiobarbituric acid in the presence of catalytic amounts of  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  as green Lewis acid through one-pot two-component strategy in ethanol at ambient temperature.

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