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$ZrOCl_2.8H_2O$ as a green and efficient catalyst for the expeditious synthesis of substituted 3-arylpyrimido[4,5-*c*]pyridazines in water

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ABSTRACT

A new and simple synthetic methodology for the preparation of 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and 3-aryl-5-oxo-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones by a one-pot three component reaction of barbituric acid or thiobarbituric acid with arylglyoxals in the presence of catalytic amount of $ZrOCl_2{\cdot}8H_2O$ as green Lewis acid and hydrazine hydrate at ambient temperature in water was reported. All of these pyrimidopyridazines derivatives have one clustered water molecule in their molecular structure. The use of $ZrOCl_2{\cdot}8H_2O$ catalyst is feasible because of its easy availability, convenient handling, high stability, simple recovery, reusability, good activity and eco-friendly.

1. Introduction

Within the past decade, green chemistry has attained the status of a major scientific discipline.[1-4] The investigation and application of green chemistry principles has led to the development of cleaner and more benign chemical processes, with many new technologies being developed each year. In today's world, synthetic chemists in both academia and industry are constantly challenged to consider more environmentally benign methods for generation of the desired target molecules.[5]

Multi-component reactions (MCRs), by virtue of their convergence, productivity, elegance, ease of execution and selectivity, have become one of the most powerful platforms to access diverse complex molecules.[6] Accordingly, these reactions have attracted considerable attention of medicinal chemistry, combinatorial synthesis,[7] pharmaceutical industry[8] and modern drug discovery and development.[9]

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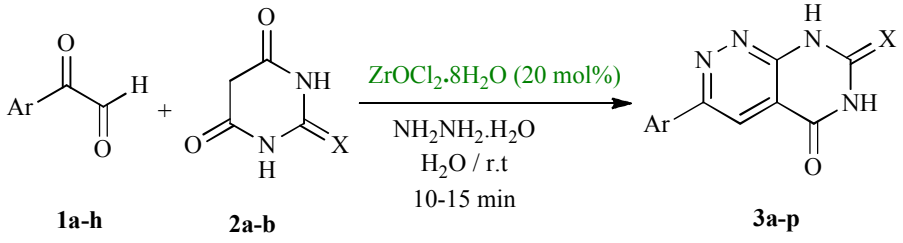
The pyridazine moiety represents a versatile scaffold to develop new pharmacologically active compounds. This azine heterocycle is included in chemicals with a wide range of biological activities and can also be used to link other pharmacophoric groups.[10] Pyridazine derivatives have biological properties and features, such as anti-viral and anti-cancer,[11] anti-hypertensive,[12] anti-inflammatory,[13] anti-microbial,[14] anti-depressant,[15] anti-HIV[16] and etc. 3-Arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones possess monoamine oxidase (MAO) inhibitory activity and substituents on the diazine nucleus modulate the inhibitory activity.[17] Monoamine oxidase (MAO) is an iron containing flavoenzyme that occurs within cells, bound to the surface membrane of mitochondria and involved in the degradation of biogenic amines. Monoamine oxidase inhibitors are the most important drugs for the clinical management of depression and Alzheimer disease.[18]

$ZrOCl_2{\cdot}8H_2O$ is a highly water–tolerant compound, which its handling does not need especial precautions. $ZrOCl_2{\cdot}8H_2O$ is a commercially available and a cheap compound. Reports on the safety of Zr(IV) salts show that their LD_{50} is high [LD_{50} [$ZrOCl_2{\cdot}8H_2O$, oral rat] = 2950 mg/kg].[19] $ZrOCl_2{\cdot}8H_2O$ with a rather high LD_{50} and low toxicity should not be expected that much harmful to mammalians. Zr^{4+} has a high charge-to-size ratio (Z^2/r, 22.22 e^2 m^{-10}) and for this reason, zirconium (IV) compounds possess a high coordinating ability that allows strong Lewis acid behavior and high catalytic activity.[20] Literature survey shows that only a very few reports are available dealing with the catalytic activity of this compound.[21-24] We now introduce $ZrOCl_2{\cdot}8H_2O$ as a new green catalyst for efficient synthesis of substituted 3-arylpyrimido[4,5-*c*]pyridazine derivatives.

2. Results and Discussion

Many organic reactions of synthetic importance are very slow and it is very important to enhance their reaction rates. The rate of the reactions can be enhanced by using a catalyst. This catalyst may be toxic in nature and it is important to find out some alternative catalyst, which is harmless or less toxic.[25] As one of our goals in this methodology is avoidance of using anti-environmental conditions, therefore, we did not apply toxic and hazardous solvents and catalyst. In the previous method,[26] that we had reported for the synthesis of 3-aryl substituted pyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and 7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones, we used pyridine as catalyst. Pyridine is a volatile, toxic and flammable liquid with a pungent and unpleasant odor. Exposure to pyridine has harmful effects on the liver, kidneys, immune systems and reproductive functions, and has potential carcinogenicity.[27-31]

Following to recent reports about the application of arylglyoxals (AG) in heterocyclic chemistry,[26,32-40] herein we have applied $ZrOCl_2{\cdot}8H_2O$ as recyclable, non-toxic and green catalyst for the regioselective synthesis of 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and their sulfur analogues in water (Scheme **1**).



Ar = C_6H_5, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$

X = O , S

Scheme 1. $ZrOCl_2{\cdot}8H_2O$ catalyzed one-pot synthesis of substituted pyrimido[4,5-*c*]pyridazines**.**

We also studied the influence of the amount of $ZrOCl_2 \cdot 8H_2O$ on the reaction yields. We found that the best yield is obtained when we used the $ZrOCl_2 \cdot 8H_2O$ 20 mol% as a catalyst. Increasing the amount of catalyst (for example 30 mol%), caused to form impure products. Utilizing the excess amount of $ZrOCl_2 \cdot 8H_2O$ cause to formation of other by-products. Also, using the amounts less than 20 mol% led to decrease the reaction yields. Therefore, the optimal amount of $ZrOCl_2 \cdot 8H_2O$ as the reaction catalyst was only 20 mol%.

The reusability of the catalyst is important from the large-scale synthesis and industrial points of view. We found that the catalyst could be separated and reused after washing with $CHCl_3$ and dried at 70 °C. The reusability of the catalyst was checked by the reaction of phenylglyoxal **1a** and barbituric acid (BA) or thiobarbituric acid (TBA) in the presence of hydrazine hydrate in water at room temperature. The results showed that the catalyst can be used effectively three times without any loss of its activity (Table **1**, entry **1** and **9**). All of the synthesized products and comparison of their obtained reaction times and yields with literature results were listed in the Table **1**.

Table 1. List of comparison of obtained results with literature data for all substituted pyrimidopyridazines

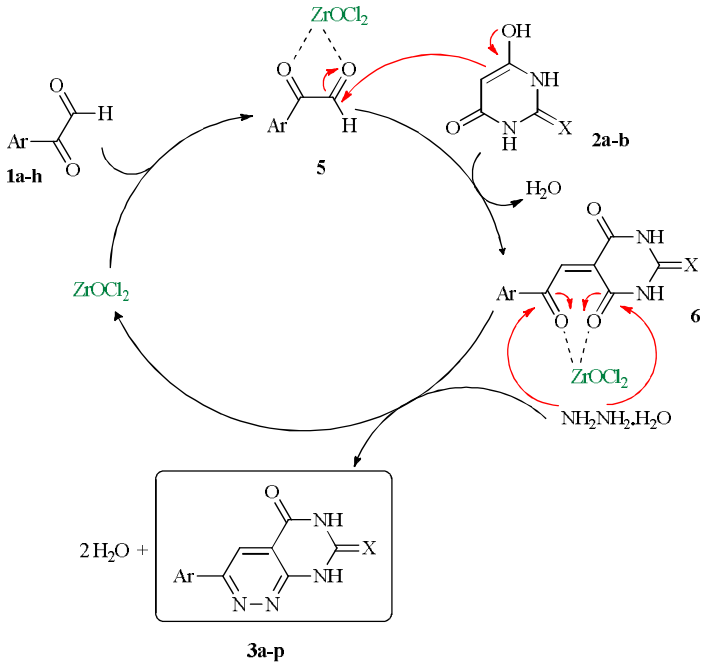
Entry	AG	BA or TBA	Products	Time (min)		Yield (%)		Mp(°C)	
				This work	Lit.[27]	This work	Lit.[27]	Found	Lit.[27]
1	**1a**	BA	**3a**	10	45	92	83	273(dec)	271(dec)
2	**1b**	BA	**3b**	12	48	89	78	258(dec)	256(dec)
3	**1c**	BA	**3c**	10	45	90	80	266(dec)	264(dec)
4	**1d**	BA	**3d**	10	45	94	91	259(dec)	257(dec)
5	**1e**	BA	**3e**	12	50	86	77	261(dec)	258(dec)
6	**1f**	BA	**3f**	15	60	78	43	330(dec)	331(dec)
7	**1g**	BA	**3g**	10	48	92	81	280(dec)	283(dec)
8	**1h**	BA	**3h**	10	50	93	78	285(dec)	282(dec)
9	**1a**	TBA	**3i**	10	49	95	94	242(dec)	240(dec)
10	**1b**	TBA	**3j**	10	50	89	74	238(dec)	235(dec)
11	**1c**	TBA	**3k**	12	55	88	65	312(dec)	315(dec)
12	**1d**	TBA	**3l**	10	48	91	77	280(dec)	278(dec)
13	**1e**	TBA	**3m**	10	52	85	73	245(dec)	243(dec)
14	**1f**	TBA	**3n**	15	60	82	46	360(dec)	362(dec)
15	**1g**	TBA	**3o**	10	58	91	83	251(dec)	254(dec)
16	**1h**	TBA	**3p**	10	55	88	70	264(dec)	262(dec)

As shown in the Table 1, by using $ZrOCl_2 \cdot 8H_2O$ as the catalyst, all these reactions proceed very fast and their obtained yields were improved.

The actual mechanism of the reaction is unclear. However, the proposed mechanism for this reaction in the presence of $ZrOCl_2 \cdot 8H_2O$ as a catalyst is shown in Scheme **2**. The arylglyoxals (**1a-h**, carbonyl groups) are firstly activated by Zr (IV) as a Lewis acid to give **5** and then the addition of barbituric acid **2a** or thiobarbituric acid **2b** to the reaction mixture leading to 1,4-dicarbonyl compound **6**. Cyclization and dehydration aromatization of compound **6** by using the hydrazine hydrate afforded the final product **3a-p**.

All products are known and were characterized by their spectral data. In the ^{1}H-NMR data, the singlet around $\delta \approx 8.5$ in all derivatives, was diagnostic of H-4 in the formed pyridazine ring. Further consideration of the ^{1}H-NMR spectra of these pyrimidopyridazines shows that there are two additional D_2O exchangeable hydrogens in all derivatives. In the case of diones **3a-h**, these hydrogens are very deshielded and they show two different signals whereas in thiones **3i-p**, the corresponding hydrogens are shielded and they show only one signal for both hydrogens. We found that these unexpected signal

belong to one clustered water molecule which is located in the molecular network of these heterocyclic systems.[32] The probable structure for the site of linking of the clustered water to the pyrimidopyridazine core was shown in the Fig.**1**.



Scheme 2. Suggested mechanism for the $ZrOCl_2 \cdot 8H_2O$ catalyzed synthesis of substituted 3-arylpyrimidopyridazines.

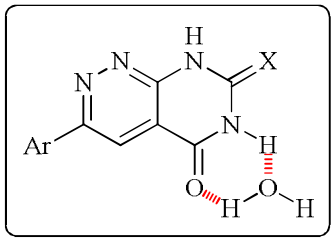


Fig. 1. Probable structure of clustered water in substituted 3-arylpyrimido[4,5-*c*]pyridazines

3. Experimental

3.1. General Procedures

Melting points were determined on a Electrothermal 9200 apparatus. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer in DMSO-d_6 with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin Elmer Spectrum Two FT-infrared spectrophotometer, measured as films or KBr disks.

3.2. General procedure for the synthesis of substituted 3-arylpyrimido[4,5-c]pyridazines

A mixture of arylglyoxal (1 mmol), barbituric acid (BA) or thiobarbituric acid (TBA) (1 mmol) and hydrazine hydrate (4 mmol) in the presence of $ZrOCl_2 \cdot 8H_2O$ (0.2mmol) as a catalyst was stirred at room temperature in water (7 mL) for 10-15 minutes. After the appropriate time, the mixture was solidified and the solid was filtered and washed with excess water (3×10 mL) and the crude material was purified by recrystallization from methanol.

3.3. Analytical data for the products

3-Phenylpyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione ***(3a)*** pink solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 14.24 (1H, bs), 11.38 (1H, s), 8.60 (1H, s), 7.91 (2H, dt, J_1 = 7.5 Hz, J_2 = 1.8 Hz), 7.76 (1H, bs), 7.55 (1H, bs), 7.48–7.54 (3H, m). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 126.3, 128.5, 129.5, 130.2, 133.2, 134.3, 145.8, 153.1, 160.7, 162.8. FT-IR (KBr) ν_{max}: 3387, 3123, 1701, 1645, 1580, 1496, 1373, 799, 621, 602 cm^{-1}.

3-(4-Bromophenyl)pyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione ***(3b)***white solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 14.28 (1H, bs), 11.36 (1H, s), 8.60 (1H, s), 7.88 (2H, d, J = 8.7 Hz), 7.73 (1H, bs),7.71 (2H, d, J = 8.7 Hz), 7.61 (1H, bs). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 123.7, 128.4, 128.6, 132.4, 133.0, 133.5, 144.8, 153.1, 160.7, 162.8. FT-IR (KBr) ν_{max}: 3417, 3122, 1723, 1701, 1649, 1594, 1570, 1492, 1396, 1371, 1244, 823, 798, 752, 620 cm^{-1}.

3-(4-Chlorophenyl)pyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione ***(3c)*** beige solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 14.27 (1H, bs), 11.35 (1H, s), 8.59 (1H, s),7.94 (2H, d, J = 8.7 Hz),7.74 (1H, bs), 7.61 (1H, bs),7.56 (2H, d, J = 8.4 Hz). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 128.2, 128.5, 129.5,133.0, 133.1, 135.0, 144.7, 153.1, 160.7, 162.8. FT-IR (KBr) ν_{max}: 3426, 3230, 3085, 1695, 1654, 1566, 1494, 1370, 1089, 836, 799, 606, 477 cm^{-1}.

3-(4-Fluorophenyl)pyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione ***(3d)*** white solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 14.22 (1H, bs), 11.37, (1H, s), 8.58 (1H, s), 7.94–7.98 (2H, m), 7.74 (1H, bs), 7.61 (1H, bs),7.30–7.36 (2H, m). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 116.3, 116.6, 128.5, 128.7, 128.8, 130.8, 130.9, 133.2, 145.0, 153.1, 160.6, 161.8, 162.8, 165.1. FT-IR (KBr) ν_{max}: 3422, 3122, 3044, 1696, 1654, 1566, 1508, 1371, 1232, 1162, 843, 610, 546 cm^{-1}.

3-(4-Methoxyphenyl)pyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione ***(3e)*** beige solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 14.08 (1H, bs), 11.44 (1H, s), 8.55 (1H, s), 7.85 (2H, d, J = 9.0 Hz), 7.75 (1H, bs), 7.60 (1H, bs), 7.05 (2H, d, J = 9.0 Hz), 3.80 (3H, s). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 55.7, 114.9, 126.7, 127.8, 128.4, 132.9, 145.6, 153.1, 160.6, 161.0, 162.9. FT-IR (KBr) ν_{max}: 3403, 3155, 2837, 1691, 1648, 1600, 1580, 1501, 1461, 1382, 1259, 1180, 1099, 831, 621, 561 cm^{-1}.

3-(4-Nitrophenyl)pyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione ***(3f)*** cream solid, ^{1}H NMR (d_6-(300 MHz, DMSO-d_6) δ: 14.45 (1H, bs), 11.27 (1H, s), 8.68 (1H, s), 8.32 (2H, d, J = 8.7 Hz), 8.18 (2H, d, J = 8.7 Hz),7.73 (1H, bs), 7.62 (1H, bs). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 124.6, 127.6, 128.2, 130.7, 140.2, 143.8, 148.3, 150.7, 160.7, 162.7. FT-IR (KBr) ν_{max}: 3414, 3288, 2943, 2901, 1694, 1654, 1566, 1517, 1496, 1368, 1350, 1234, 1098, 861, 609 cm^{-1}.

3-(3,4-Dimethoxyphenyl)pyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione ***(3g)***yellow solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 14.09 (1H, bs), 11.43 (1H, s), 8.59 (1H, s), 7.75 (1H, bs), 7.61 (1H, bs),7.48 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5Hz), 7.44 (1H, d, J = 1.8 Hz), 7.06 (1H, d, J = 8.1 Hz), 3.82 (3H, s), 3.80 (3H, s). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 56.0, 56.1, 109.2, 112.3, 119.4, 126.8, 133.1, 145.7, 149.6, 150.8, 153.1, 160.6, 163.0. FT-IR (KBr) ν_{max}: 3388, 3226, 2998, 1717, 1697, 1633, 1578, 1504, 1422, 1363, 1296, 1258, 1216, 1158, 1022, 801, 603, 523 cm^{-1}.

3-(Benzo[d][1,3]dioxol-5-yl)pyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione ***(3h)*** yellow solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 14.11 (1H, bs), 11.40 (1H, s), 8.53 (1H, s), 7.74 (1H, bs), 7.60 (1H, bs),7.41–7.44 (2H, m), 7.03 (1H, d, J = 8.7 Hz), 6.09 (2H, s). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 102.1, 106.2, 109.1, 121.1, 128.3, 128.4, 133.1, 145.5, 148.6, 149.1, 153.1, 160.6, 162.9. FT-IR (KBr) ν_{max}: 3402, 3199, 2900, 1701, 1649, 1595, 1501, 1446, 1374, 1229, 1038, 617, 555 cm^{-1}.

3-Phenyl-7-thioxo-7,8-dihydropyrimido[4,5-c]pyridazin-5(6H)-one ***(3i)*** pale yellowsolid, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 13.92 (1H, bs), 10.47 (1H, s), 8.49 (1H, s), 7.88 (2H, dt, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.47–7.51 (3H, m), 4.90 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 126.2, 128.3, 129.5, 130.0,

131.0, 134.6, 145.6, 159.9, 160.6, 163.5. FT-IR (KBr) ν_{max}: 3353, 3152, 3065, 1692, 1661, 1577, 1532, 1217, 699, 601 cm^{-1}.

3-(4-Bromophenyl)-7-thioxo-7,8-dihydropyrimido[4,5-c]pyridazin-5(6H)-one ***(3j)*** beige solid, ^1H NMR (300 MHz, DMSO-d_6) δ: 13.89 (1H, bs), 10.45 (1H, s), 8.69 (1H, s), 8.48 (1H, s), 7.85 (2H, d, *J* = 8.4 Hz), 7.69 (2H in one tautomer, d, *J* = 8.4 Hz), 4.89 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 121.6, 123.5, 125.7, 128.4, 129.6, 130.2, 130.9, 131.3, 131.7, 132.2, 132.4, 133.8, 137.2, 144.6, 159.8, 160.5, 188.9. FT-IR (KBr) ν_{max}: 3364, 3172, 3032, 1681, 1644, 1596, 1493, 1399, 1218, 1011, 830, 754, 592 cm^{-1}.

*3-(4-Chlorophenyl)-7-thioxo-7,8-dihydropyrimido[4,5-c]pyridazin-5(6H)-one****(3k)*** white solid, ^1H NMR (300 MHz, DMSO-d_6) δ: 13.88 (1H, bs), 10.44 (1H, s), 8.49 (1H, s), 7.93 (2H, d, *J* = 8.4 Hz), 7.56 (2H, d, *J* = 8.4 Hz),4.89 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 128.1, 129.5, 129.6, 130.9, 131.5, 133.4, 134.8, 144.5, 159.8, 160.5. FT-IR (KBr) ν_{max}: 3170, 3033, 1682, 1591, 1528, 1496, 1404, 1090, 1015, 832, 593 cm^{-1}.

*3-(4-Fluorophenyl)-7-thioxo-7,8-dihydropyrimido[4,5-c]pyridazin-5(6H)-one****(3i)*** cream solid, ^1H NMR (300 MHz, DMSO-d_6) δ: 13.92 (1H, bs), 10.46 (1H, s), 8.48 (1H, s), 7.93–7.98 (2H, m), 7.30–7.36 (2H, m),4.89 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 116.2, 116.5, 128.6, 128.7, 129.6, 131.1, 131.2, 144.8, 159.8, 160.4, 161.7, 165.0. FT-IR (KBr) ν_{max}: 3224, 3105, 3055, 1701, 1601, 1514, 1460, 1244, 1159, 921, 837, 551 cm^{-1}.

*3-(4-Methoxyphenyl)-7-thioxo-7,8-dihydropyrimido[4,5-c]pyridazin-5(6H)-one****(3m)*** pale green solid, ^1H NMR (300 MHz, DMSO-d_6) δ: 13.83 (1H, bs), 10.50 (1H, s), 8.45 (1H, s), 7.84 (2H, d, *J* = 9.0 Hz), 7.05 (2H, d, *J* = 9.0 Hz), 4.88 (s, 2H), 3.80 (3H, s). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 55.7, 114.9, 127.0, 127.7, 128.4, 129.4, 130.9, 145.4, 160.0, 160.4, 160.8. FT-IR (KBr) ν_{max}: 3423, 3321, 3016, 2935, 2841, 1689, 1669, 1637, 1609, 1589, 1577, 1514, 1253, 1176, 1022, 831, 566cm^{-1}.

*3-(4-Nitrophenyl)-7-thioxo-7,8-dihydropyrimido[4,5-c]pyridazin-5(6H)-one****(3n)*** beige solid, ^1H NMR (300 MHz, DMSO-d_6) δ: 14.13 (1H, bs), 10.41 (1H, s), 8.58 (1H, s), 8.33 (2H, d, *J* = 8.7 Hz), 8.18 (2H, d, *J* = 8.7 Hz), 4.91 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 124.6, 127.5, 127.6, 129.6, 131.1, 140.6, 143.7, 148.2, 159.7, 160.5. FT-IR (KBr) ν_{max}: 3414, 3288, 2943, 2901, 1694, 1654, 1566, 1517, 1496, 1368, 1350, 1234, 1098, 861, 609cm^{-1}.

*3-(3,4-Dimethoxyphenyl)-7-thioxo-7,8-dihydropyrimido[4,5-c]pyridazin-5(6H)-one****(3o)*** pale yellow solid, ^1H NMR (300 MHz, DMSO-d_6) δ: 13.83 (1H, bs), 10.49 (1H, s), 8.47 (1H, s), 7.43–7.46 (2H, m), 7.05 (1H, d,*J* = 8.4 Hz), 4.88 (s, 2H), 3.82 (3H, s), 3.80 (3H, s). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 56.0, 56.1, 109.1, 112.2, 119.3, 127.1, 129.4, 131.0, 145.5, 149.5, 150.6, 160.0, 160.4. FT-IR (KBr) ν_{max}: 3319, 3251, 2996, 2937, 1682, 1638, 1584, 1519, 1466, 1382, 1266, 1228, 1137, 1020, 845, 597cm^{-1}.

*3-(Benzo[d][1,3]dioxol-5-yl)-7-thioxo-7,8-dihydropyrimido[4,5-c]pyridazin-5(6H)-one****(3p)***pale green solid, ^1H NMR (300 MHz, DMSO-d_6) δ: 13.82 (1H, bs), 10.46 (1H, s), 8.42 (1H, s), 7.38–7.41 (2H, m), 7.02 (1H, d, *J* = 8.7 Hz), 6.09 (2H, s),4.87 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 102.0, 106.2, 109.0, 120.8, 128.7, 129.4, 131.1, 145.3, 148.6, 149.0, 159.9, 160.4. FT-IR (KBr) ν_{max}: 3317, 3238, 3058, 2917, 1685, 1663, 1572, 1508, 1491, 1443, 1254, 1231, 1033, 886, 556cm^{-1}.

4. Conclusions

In summary, we have demonstrated the efficiency of $ZrOCl_2 \cdot 8H_2O$, for the preparation of 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and 3-aryl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones by a one-pot three component reaction. The notable special features of this methodology are the simple reaction procedure, shorter reaction time, good to excellent yields of

products, high purity of the products, ready availability, low cost, low toxicity, moderate Lewis acidity, moisture compatibility of the catalyst and recycle ability. Thus, this methodology represents a better, eco-friendly alternative to many existing procedures and is also suitable for industrial application.

Supporting Information

IR, ^{1}HNMR and ^{13}CNMR spectra of all substituted 3-arylpyrimido[4,5-*c*]pyridazines are available on the Current Chemistry Letters website at http://www.GrowingScience.com/ccl/Vol4/SP_ccl_2015_13.pdf.

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