Article

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# Solvent-free Synthesis of Novel and Known Octahydroquinazolinones/thiones by the Use of $ZrOCl_2.8H_2O$ as a Highly Efficient and Reusable Catalyst

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A solvent-free reaction between urea/thiourea, dimedone and aromatic aldehydes in the presence of catalytic amounts of zirconium (IV) oxychloride octahydrate ($ZrOCl_2.8H_2O$) as a powerfull Lewis acid leads to octahydroquinazolinone/thione derivatives in good yields. This method has advantages such as avoidance of the organic solvents, production of pure products without any by-product, short reaction times and simple operation.

**Keywords:** Octahydroquinazolinone/thione; $ZrOCl_2.8H_2O$; Urea/thiourea; Aromatic aldehyde.

## INTRODUCTION

In the last two decades, multicomponent reactions (MCRs) have drawn special attention due to the advent of high-throughput screening techniques that enabled rapid identification of potential new medicines among large collections of organic compounds.[1-4] Moreover, the chemistry of quinazoline system has received an increasing interest because of its biological significance. They are a class of drugs which function as hypnotic/sedatives. For example, the *Afloqualone*, *Cloroqualone*, and *Diproqualone* (Fig. 1) have been used in the treatment of cancer.[5]

The most general method for the preparation of octahydroquinazolinones/thiones involves the one-pot Biginelli condensation reaction of cyclic 1,3-dione, aromatic aldehydes and urea/thiourea in the presence of a Lewis or mineral acids. Although the synthesis of octahydroquinazolinones/thiones via the Biginelli reaction by the use of several reagents have been reported until now, most of these procedures have disadvantages such as, long reaction time, use of strongly acidic condition or organic solvents, unsatisfactory product yield, and also side products.[6-11] Among the common Lewis acids, the zirconium (IV) oxychloride octahydrate has been considered as a safe potential catalyst in recent organic synthesis[13-18] due to its low toxicity [LD50 ($ZrOCl_2.8H_2O$) oral rate = 2950 mg/kg],[12] low costs, ease of handling, and high activity.

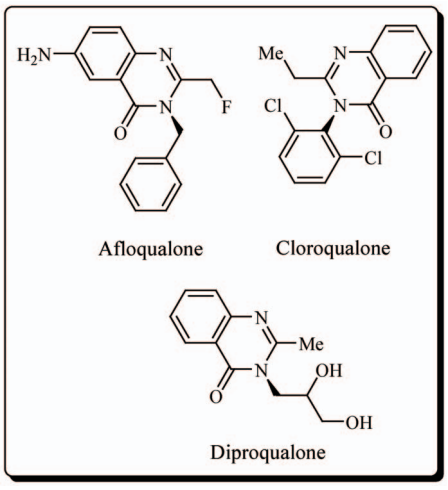


Fig. 1. Quinazolinene derivatives as anti cancer compounds.

## EXPERIMENTAL

### General

All chemicals were purchased from Merck, Fluka and Aldrich. The reactions were monitored by TLC (silica gel 60 $F_{254}$, hexane/EtOAc). IR spectra were recorded on a FT-IR JASCO-680 and the NMR spectra were obtained on a Bruker-Instrument DPX-400 MHz Avance 2 model. The varioEl CHNS Isfahan Industrial University was used for elemental analysis.

### Preparation of octahydroquinazolinones/thiones

A mixture of urea/thiourea (1.2 mmol), aldehyde (1 mmol), cyclic 1,3-dione (1 mmol), and $ZrOCl_2.8H_2O$ (10 mol%) was stirred and heated at 100 °C in a preheated oil bath for an appropriate time (Table 2). After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and dichloromethane (10 mL) was added. Then the resulting mixture was stirred for 3

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min. The catalyst was separated by filtration. The solvent was removed by distillation, then washed with cold water and recrystallized from methanol to afford the pure product.

**Compound 4b**

IR (KBr): 3285 (s), 3200 (s), 1640 (s), 1605 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 0.911 (3H, s, $CH_3$), 1.041 (3H, s, $CH_3$), 1.97-2.19 (2H, m, $CH_2$), 2.30-2.51 (2H, m, $CH_2$), 3.66 (3H, s, $OCH_3$), 4.76 (1H, s, CH), 7.07-6 (m, 4H, Arom), 7.76 (1H, s, NH), 9.27 (1H, s, NH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) δ: 27.34 ($CH_3$), 29.16 ($CH_3$), 31.56 (C), 32.75 ($CH_2$), 50.52 ($CH_2$), 51.84 (CH), 55.29 ($OCH_3$), 107.84 (C), 113.39 (CH), 128.99 (CH), 135.15 (C), 149.52 (C), 153.61 (C), 157.55 (CO), 194.86 (CO) ppm; Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33%. Found: C, 68.228; H, 6.41; N, 9.25%.

**Compound 4c**

IR (KBr): 3443 (s), 3192 (s), 1681 (s), 1665 (s), 1624 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 0.74 (3H, s, $CH_3$), 0.81 (3H, s, $CH_3$), 1.75-1.93 (2H, m, $CH_2$), 2.09-2.24 (2H, m, $CH_2$), 5.34 (1H, s, CH), 7.05-7.18 (4H, m, Arom), 7.50 (1H, s, NH), 9.33 (1H, s, NH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) δ: 28.64 ($CH_3$), 30.33 (C), 33.85 ($CH_2$), 51.38 (CH), 107.41 (C), 128.99 (CH), 130.55 (CH), 131.01 (CH), 133.46 (CH), 142.79 (CH), 154.66 (C), 161.84 (CO), 194.24 (CO) ppm; Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19%. Found: C, 63.26; H, 5.37; N, 9.12%.

**Compound 4h**

IR (KBr): 3285 (s), 3190 (s), 1646 (s), 1605 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 0.79 (3H, s, $CH_3$), 0.879 (3H, s, $CH_3$), 1.93-1.97 (2H, d, $J$ = 16 Hz, $CH_2$), 2.00-2.04 (2H, d, $J$ = 16 Hz, $CH_2$), 2.26 (1H, s, $CH_3$), 4.50 (1H, s, CH), 6.80-6.98 (4H, m, Arom), 7.06 (2H, br, NH) ppm; Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85%. Found: C, 72.03; H, 6.90; N, 9.72%.

**Compound 4j**

IR (KBr): 3228 (s), 2962 (s), 1649 (s), 1620 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 1.89-1.83 (2H, m, $CH_2$), 1.94-2.00 (2H, m, $CH_2$), 2.30-2.34 (2H, m, $CH_2$), 4.594 (1H, s, CH), 7.09-7.24 (5H, m, Arom), 7.51 (1H, s, NH), 9.34 (1H, s, NH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) δ: 21.00 ($CH_2$), 27.77 ($CH_2$), 36.75 ($CH_2$), 50.94 (CH), 107.69 (C), 113.39 (CH), 129.03 (CH), 136.07 (C), 149.51 (C), 154.81 (C), 158.74 (CO), 191.82 (CO) ppm; Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56%. Found: C, 69.22; H, 5.92; N, 11.41%.

**Compound 4n**

IR (KBr): 3302 (s), 3190 (s), 1688 (s), 1667 (s), 1636 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 1.35-1.61 (2H, m, $CH_2$), 1.74-1.91 (2H, m, $CH_2$), 1.96-2.18 (2H, m, $CH_2$), 3.50 (1H, s, $OCH_3$), 4.39 (1H, s, CH), 6.56-6.65 (4H, m, Arom), 6.96 (1H, s, NH), 8.11 (1H, s, NH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) δ: 20.99 ($CH_2$), 29.00 ($CH_2$), 37.27 ($CH_2$), 55.02 (CH), 101.62 (C), 110.42 (CH), 111.48 (CH), 119.84 (CH), 126.56 (CH), 129.25 (CH), 131.70 (CH), 156.55 (C), 169.11 (CO), 196.02 (CO) ppm; Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29%. Found: C, 66.40; H, 5.752; N, 10.11%.

**Compound 4q**

IR (KBr): 3437 (s), 3305 (s), 1664 (s), 1613 (s), 1589 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 0.679 (3H, s, $CH_3$), 0.803 (3H, s, $CH_3$), 1.82-2.01 (2H, m, $CH_2$), 2.06-2.22 (2H, m, $CH_2$), 4.94 (1H, s, CH), 7.06-7.16 (4H, m, Arom), 7.61 (1H, s, NH), 9.35 (1H, s, NH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) δ: 27.28 ($CH_3$), 29.12 (C), 32.78 ($CH_2$), 50.21 ($CH_2$), 52.08 (CH), 107.25 (C),125.32 (CH), 126.25 (CH), 127.35 (CH), 130.48 (CH), 133.26 (CH), 145.90 (CH), 147.42 (C), 158.11 (CO), 193.03 (CO) ppm; Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19%. Found: C, 63.22; H, 5.55; N, 9.08%.

**Compound 4r**

IR (KBr): 3278 (s), 3162 (s), 1642 (s), 1572 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 0.903 (3H, s, $CH_3$), 1.04 (3H, s, $CH_3$), 2.09-2.05 (2H, m, $CH_2$), 2.21 (2H, s, $CH_2$), 2.24 (3H, s, $CH_3$), 5.13 (1H, s, CH), 7.09-7.15 (m, 4H, Arom), 9.65 (1H, s, NH), 10.55 (1H, s, NH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) δ: 20.33 ($CH_3$), 27.34 ($CH_3$), 29.60 ($CH_3$), 32.75 (C), 37.84 ($CH_2$), 50.75 ($CH_2$), 51.51 (CH), 105.84 (C), 123.29 (CH), 129.00 (CH), 137.37 (C), 140.00 (C), 149.47 (C), 174.61 (CS), 195.06 (CO) ppm; Anal. Calcd. for $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71; N, 9.32; S, 10.67%. Found: C, 68.18; H, 6.50; N, 9.21; S, 10.45%.

**Compound 4t**

IR (KBr): 3262 (s), 3165 (s), 1666 (s), 1641 (s), 1584 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 0.90 (3H, s, $CH_3$), 1.03 (3H, s, $CH_3$), 2.08-2.21 (2H, m, $CH_2$), 2.35-2.47 (2H, q, $J$ = 16 Hz, $CH_2$), 3.72 (3H, s, $OCH_3$), 5.12 (1H, s, CH), 6.88-6.91 (2H, m, Arom), 7.14-7.12 (2H, m, Arom), 9.64 (1H, s, NH), 10.54 (1H, s, NH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) δ: 27.25 ($CH_3$), 29.29 ($CH_3$), 32.73 (C), 38.93 ($CH_2$), 50.31 ($CH_2$), 52.09 (CH), 55.56 ($OCH_3$),

108.75 (C), 114.27 (CH), 128.09 (CH), 136.06 (C), 148.92 (C), 159.09 (C), 174.82 (CS), 194.11 (CO) ppm; Anal. Calcd. for $C_{17}H_{20}N_2O_2S$: C, 64.53; H, 6.37; N, 8.85; S, 10.13%. Found: C, 64.61; H, 6.39; N, 8.72; S, 9.90%.

**Compound 4u**

IR (KBr): 3262 (s), 3173 (s), 1698 (s), 1620 (s), 1567 (s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ: 0.897 (3H, s, $CH_3$), 1.035 (3H, s, $CH_3$), 2.059-2.229 (2H, m, $CH_2$), 2.364-2.484 (2H, m, $CH_2$), 5.193 (1H, s, CH), 7.22-7.28 (m, 2H, Arom), 7.32-7.36 (2H, m, Arom), 9.69 (1H, s, NH), 10.59 (1H, s, NH) ppm; $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) δ: 27.24 ($CH_3$), 29.28 (C), 32.73 ($CH_2$), 50.31 ($CH_2$), 52.69 (CH), 108.61 (C), 126.89 (CH), 128.02 (CH), 128.96 (CH), 143.83 (CH), 149.16 (C), 175.08 (CS), 194.12 (CO) ppm; Anal. Calcd. for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78; S, 11.20%. Found: C, 67.22; H, 6.40; N, 9.65; S, 11.35%.

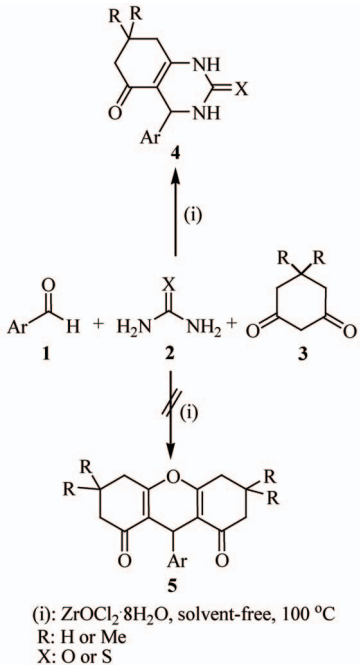
## RESULTS AND DISCUSSION

Nowadays, the use of catalysts in chemical industries and academic researches has been extensively studied.[19-21] In connection with our previous programs on synthesis of organic compounds using safe catalysts,[21-24] in this work, we wish to report a simple and convenient synthesis of octahydroquinazolinones/thiones **4** by reaction of aromatic aldehyde **1**, urea/thiourea **2**, and cyclic 1,3-dione **3**, in the presence of catalytic amount of $ZrOCl_2.8H_2O$ under solvent-free conditions (Scheme I). The yield of products was good to excellent without the formation of octahydoxanthenes **5**, which is the major product of the procedure reported by the literature.[25]

The need to implement green chemistry principles (*e.g.* safer solvents, less hazardous chemical synthesis, atom economy and catalysis) is a driving force towards the avoidance of organic solvents and use of cheap, environmentally friendly, and reusable catalyst. A solvent-free or solid state reaction obviously reduce pollution and cost due to simplification of experimental procedure, work up technique, and saving in labour. However, interest in the environmental control of chemical processes has increased remarkably during three decades ago as a response to public concern about the use of hazardous chemicals. Therefore, to improve the effectiveness of this method in preventing chemical waste, it is important to investigate optimal reaction conditions.

To exploit simple and suitable conditions for the preparation of **4** using $ZrOCl_2.8H_2O$ as a powerful Lewis acid catalyst, the treatment of benzaldehyde, dimedone, and urea was chosen as a model reaction. At first, we found that in the absence of $ZrOCl_2.8H_2O$, the reaction did not proceed even at a high temperature after long reaction time. After examining the various amounts of $ZrOCl_2.8H_2O$ and a wide range of temperatures (Table 1), we found that the reaction can be efficiently carried out by adding 10 mol% of the catalyst at 100 °C under solvent-free conditions in a short time span of 50 min. The use of excessive amounts of the catalyst does not increase the product yield or reaction rate.

**Scheme I** Three-component condensation of arylaldehydes, cyclic 1,3-dione, and urea/thiourea using $ZrOCl_2.8H_2O$ as catalyst




In order to prove the versatility of this method, we extended these reaction conditions to a series of arylaldehydes (Table 2), in this process. Both electron-donating and electron-withdrawing groups on the arylaldehyde reacted well to afford the corresponding products **4** in good to excellent yields.

In view of eco-friendly procedure, the recovery and reuse of this catalyst is quite preferable. Zirconium (IV) oxychloride octahydrate was easily separated from the reaction mixture by filtering, followed by drying at room temperature. The catalyst was reused three times for synthesis of **4a** without significant loose of activity.

Table 1. Optimization of reaction conditions

| Entry | Catalyst (mol%)/ Temperature (°C) | Time (min) | Yield[a] (%) |
|---|---|---|---|
| 1 | -/25 | 360 | trace |
| 2 | -/60 | 360 | 10 |
| 3 | -/100 | 360 | 25 |
| 4 | -/150 | 360 | 25 |
| 5 | 10/25 | 360 | 40 |
| 6 | 10/60 | 360 | 70 |
| 7 | 10/90 | 120 | 80 |
| 8 | 10/100 | 50 | 90 |
| 9 | 10/130 | 70 | 75 |
| 10 | 15/100 | 70 | 90 |
| 11 | 20/100 | 70 | 80 |
| 12 | 5/110 | 240 | 80 |
| 13 | 5/130 | 180 | 80 |
| 14 | 3/100 | 360 | 70 |
| 15 | 3/130 | 360 | 65 |

[a] Isolated yields.

Table 2. Synthesis of **4** via the Biginelli method using $ZrOCl_2.8H_2O$ at 100 °C under solvent-free conditions

| Entry | R | Ar | X | Time (min) | Yield[a] (%) | M.p. (°C) |
|---|---|---|---|---|---|---|
| **4a** | Me | $C_6H_5$ | O | 50 | 90 | 288-290 |
| **4b** | Me | 4-MeO-$C_6H_4$ | O | 50 | 80 | 272-274 |
| **4c** | Me | 2-Cl-$C_6H_4$ | O | 50 | 85 | 271-273 |
| **4d** | Me | 4-Br-$C_6H_4$ | O | 30 | 80 | 324-326 |
| **4f** | Me | 4-F-$C_6H_4$ | O | 40 | 78 | 300-302 |
| **4g** | Me | 2-MeO-$C_6H_4$ | O | 30 | 85 | 197-199 |
| **4h** | Me | 4-Me-$C_6H_4$ | O | 30 | 90 | 300-302 |
| **4i** | Me | 3-$O_2N$-$C_6H_4$ | O | 25 | 90 | 297-299 |
| **4j** | H | $C_6H_5$ | O | 45 | 90 | 275-277 |
| **4k** | H | 4-Cl-3-$O_2N$-$C_6H_3$ | O | 20 | 85 | 209-211 |
| **4l** | H | 4-Br-$C_6H_4$ | O | 35 | 80 | 275-277 |
| **4m** | H | 4-Cl-$C_6H_4$ | O | 40 | 85 | 281-282 |
| **4n** | H | 2-MeO-$C_6H_4$ | O | 30 | 80 | 197-199 |
| **4o** | Me | 2,4-$Cl_2$-$C_6H_3$ | O | 30 | 85 | 263-265 |
| **4p** | Me | 3-Br-$C_6H_4$ | O | 25 | 90 | 265-267 |
| **4q** | Me | 3-Cl-$C_6H_4$ | O | 45 | 80 | 290-292 |
| **4r** | Me | 4-Me-$C_6H_4$ | S | 35 | 85 | 280-282 |
| **4s** | Me | 4-Br-$C_6H_4$ | S | 90 | 75 | 290-292 |
| **4t** | Me | 4-MeO-$C_6H_4$ | S | 65 | 80 | 268-270 |
| **4u** | Me | $C_6H_5$ | S | 90 | 80 | 280-282 |

[a] Isolated yields.

## CONCLUSIONS

In this study, a rapid and modified method for the one-pot reaction of aldehydes, cyclic 1,3-dione and urea/thiourea by employing the $ZrOCl_2.8H_2O$ as commercially available catalyst under solvent-free conditions has been described. This simple catalytic system is remarkably tolerant to a variety of functional groups on the arylaldehyde and offers significant advantages such as, low catalyst loading, high yields, short reaction times, operational simplicity, and avoidance of the organic solvents. Therefore, in employing a small amount of safe, inexpensive, and powerful catalyst under solvent-free conditions, this protocol is economic and eco-friendly.

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