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Research Article

Selective Solvent-Free Biginelli Condensation using Tungstate Sulfuric Acid as Powerful and Reusable Catalyst

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Abstract

Tungstate sulfuric acid (TSA) has been prepared and used as a recyclable catalyst for the Biginelli synthesis of some biologically active quinazolinones/thiones under solvent-free conditions. This method has advantages such as the avoidance of organic solvents, high yield of pure products, short reaction times, and operational simplicity.

Keywords: Biginelli; Tungstate sulfuric acid; Quinazolinones/thiones; Solvent-Free

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1. Introduction

Using solid acid catalysts have attracted a great degree of academic interest [1-6]. More recently, pressure from environmentalists has led to a search for more environmentally friendly forms of catalysis [7,8]. In the last two decades, multicomponent reactions (MCRs) have also 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 [9,10]. To exemplify, 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* have also been used in the treatment of cancer [11]. In addition, some octahydroquinazolinone derivatives have been used as biologically active compounds against staphylococcus aureus, escherichia coli, pseudomonas aeruginosa [12] and also as a calcium antagonist activity [13].

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, synthesis of octahydroquinazolinones/thiones via the Biginelli reaction have been reported using several reagents, most of the current procedures have disadvantages such as, long reaction time, the use of strongly acidic condition or organic solvents, unsatisfactory product yield, and side products [14-19]. There are also examples of

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successful Biginelli reactions [20-22].

2. Materials and Methods

The chemicals were purchased from Merck, Fluka and Aldrich chemical companies. The reactions were monitored by TLC (silica-gel 60 F254, hexane: AcOEt). IR spectra were recorded on a FT-IR Shimadzu-470 spectrometer. 1H and 13C NMR spectra were obtained on a Bruker-Instrument DPX-400 Avance 2, operating at 400MHz for 1H, and 100MHz for 13C respectively. X-ray diffraction (XRD) pattern was obtained by a Philips X Pert Pro X diffractometer operated with an Nifiltered CuKα radiation source 9. X-ray fluorescence (XRF) spectra were recorded by an X-ray fluorescence analyzer, Bruker, S4. The varioEl CHNS was also used for elemental analysis.

2.1. General Procedure for the Preparation of TSA(1)

At first, 25 ml of dry *n*-hexane was taken in a 100 ml round bottom flask, equipped with ice bath and overhead stirrer, and 5.876 g (2 mmol) of anhydrous sodium tungstate was added to the flask, then 0.266 ml (4 mmol) of chlorosulfonic acid was added dropwise to the flask during 30 min. This solution was stirred for 1.5 h. Afterwards the reaction mixture was gradually poured into 25 ml of chilled distilled water with agitation. The yellowish solid which separated out was filtered. Then the catalyst was washed with distilled water for five times till the filtrate showed negative test for chloride ion, and was dried at 120 °C about 5 h. The catalyst was obtained in 98% yield as a bluish solid, which decomposed at 285 °C.

2.2. Methods

A mixture of urea/thiourea (1.2 mmol), aldehyde (1 mmol), cyclic 1,3-dione (1 mmol), and TSA (0.1 mmol) 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 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 5.

Spectral data of novel compounds

Compound **5b:** IR (KBr) υ_{max} / cm^{-1}: 3285 (s), 3200 (s), 1640 (s), 1605 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 0.91 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.99 (1H, d, J = 16 Hz, CH_2), 2.18 (1H, d, J = 16 Hz, CH_2(1) 2.32 ,H, d, J = 16 Hz, CH_2), 2.49 (1H, d, J = 16 Hz, CH_2), 3.66 (3H, s, OCH_3), 4.76 (1H, s, CH), 7.07-6.86 (m, 4H, Arom), 7.76 (1H, s, NH), 9.27 (1H, s, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ / ppm : 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 **5c**: IR (KBr) υ_{max} / cm^{-1}: 3443 (s), 3192 (s), 1681 (s), 1665 (s), 1624 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 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 / ppm : 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 **5h**: IR (KBr) υ_{max} / cm^{-1}: 3285 (s), 3190 (s), 1646 (s), 1605 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 0.79 (3H, s, CH_3), 0.87 (3H, s, CH_3), 1.95 (2H, d, J = 16 Hz, CH_2), 2.02 (2H, d, J = 16 Hz, CH_2), 2.26 (3H, 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 **5j**: IR (KBr) υ_{max} / cm^{-1}: 3228 (s), 2962 (s), 1649 (s), 1620 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 1.89-1.83 (2H, m, CH_2) ,1.94 -2.00 (2H, m, CH_2) 2) 2.34- 2.30 ,H, m, CH_2), 4.59 (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 / ppm : 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 **5n**: IR (KBr) υ_{max} / cm^{-1}: 3302 (s), 3190 (s), 1688 (s), 1667 (s), 1636 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 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 (3H, 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 / ppm : 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 **5q**: IR(KBr) υ_{max} / cm^{-1}: 3437 (s), 3305 (s), 1664 (s), 1613 (s), 1589 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 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 / ppm : 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 **5r**: IR (KBr) υ_{max} / cm^{-1}: 3278 (s), 3162 (s), 1642 (s), 1572 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 0.90 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.05-2.09 (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 / ppm : 20.33 (CH_3), 27.34 (CH_3), 29.60 (CH_3), 32.75 (C), 37.84 (CH2), 50.75 (CH2), 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 **5t**: IR (KBr) υ_{max} / cm^{-1}: 3262 (s), 3165 (s), 1666 (s), 1641 (s), 1584 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 0.90 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.08-2.21 (2H, m, CH_2), 2.39-2.43 (2H, m, CH_2), 3.72 (3H, s, OCH_3), 5.122 (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 / ppm : 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 **5u**: IR (KBr) υ_{max} / cm^{-1}: 3262 (s), 3173 (s), 1698 (s), 1620 (s), 1567 (s); ^1H NMR (DMSO-d_6, 400 MHz) δ / ppm : 0.89 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.05-2.22 (2H, m, CH_2), 2.36-2.48 (2H, m, CH_2), 5.19 (1H, s, CH), 7.22-7.28 (m, 3H, 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 / ppm : 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 %.

Table 1. XRF data of TSA 1

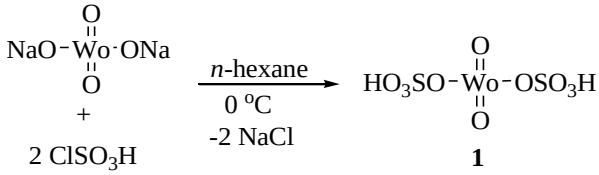
Compound	Concentration, %W/W
WO_4	19.49
SO_3	0.317
Na_2O	0.190
Cl	0.056
CuO	0.023
Fe_2O_3	0.015
CaO	0.014
LOI*	79.82
Total	99.93

* Loss on Ignition

3. Results and Discussion

In connection with our previous programs on the synthesis of organic compounds using safe catalysts [23-25], here, tungstate sulfuric acid (TSA **1**) was prepared from sodium tungstate and chlorosulfonic acid (Scheme 1). The reaction is simple and proceeds efficiently to produce the desired solid acid. TSA (**1**) was characterized by X-ray fluorescence (XRF), X-ray diffraction (XRD), and FT-IR spectroscopy [26,27].

Figure 1 shows the XRD patterns of tungstate sulfuric acid (**1**). It was reported that high degree mixing of W–S in chlorosulfonic acid often led to the absence of XRD pattern for anhydrous sodium tungstate [28]. The broad peak around 25.7° (2 θ) (θ is the Bragg's angle) from the smaller inset could be attributed to inser-



Scheme 1. Synthesis of tungstate sulphuric acid (TSA).

tion of W into the framework of chlorosulfonic acid. The XRF data of TSA **1** indicates the presence of WO_4 and SO_3 in this catalyst (Table 1).

The FT-IR spectra of anhydrous sodium tungstate and TSA **1** are shown in Figure 2. The spectrum of TSA (**1**) shows the characteristic bonds of anhydrous sodium tungstate and chlorosulfonic acid. The absorption in 3406, 1820, 1725, 1702, 1620, 1290, 1060, 1005 and 860 cm^{-1} in the catalyst spectrum reveal both bonds in anhydrous sodium tungstate and $-OSO_3H$ group.

In this work, we wish to report a simple and convenient synthesis of octahydroquinazolinones/thiones **5** by the reaction of aromatic aldehyde **2**, urea/thiourea **3**, and cyclic 1,3-diones **4** in the presence of catalytic amount of TSA (**1**) under solvent-free conditions (Scheme 2). The yields of the products were good to excellent without the formation of octahydoxanthenes **6**, which is the major product of the procedure reported by the literature [29]. According to some reports in the literature [7], the octahydoxanthenes **6** can be formed from the reaction of aldehydes with cyclic 1,3-diones **4** under catalytic conditions. The present TSA-catalyzed method showed the good selectivity towards desired product **5**.

A solvent-free or solid state reaction obviously reduce pollution, and bring down handling costs due to simplification of experimental procedure, work up technique and saving in labour. To improve the effectiveness of this method in preventing chemical waste, it is important to investigate optimal reaction conditions. To find the simple and suitable conditions for the preparation of **5** using TSA (**1**), the treatment of benzaldehyde, dimedone, and urea was chosen as a model reaction. At first, we found that in the absence of **1**, the reaction did not proceed even at a high temperature after a long reaction time. Examining the various amounts of **1** and a wide range of temperatures revealed that this reaction can be efficiently carried out by adding 10 mol% of catalyst at 100 °C under solvent-free conditions. The use of excessive amounts of the catalyst did not increase the product yield or reaction rate.

The scope of this MCR was examined using a variety of aromatic aldehydes. It was found that both electron rich and electron poor aldehydes reacted well to afford the corresponding products **5** in good to excellent yields. The obtained results are summarized in Table 2.

In view of the importance of the eco-friendly procedures, the recovery and reuse of this catalyst is quite preferable. TSA (**1**) was easily separated from the reaction mixture by filtering, followed by drying. The catalyst was reused four times in synthesis of **5a** without significant loss in catalytic activity (Figure 3).

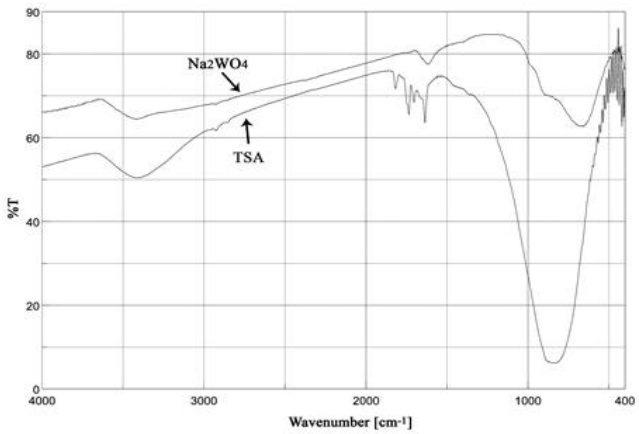


Figure 2. FT-IR spectra of TSA 1.

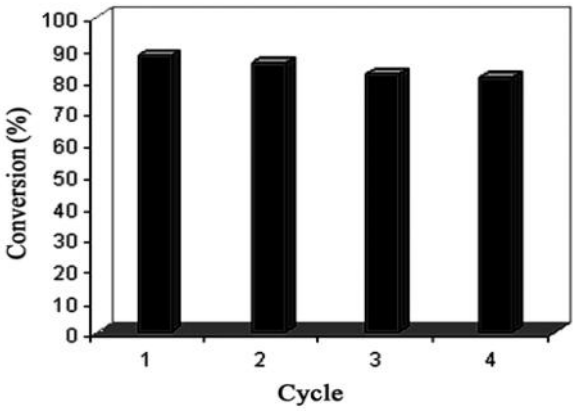
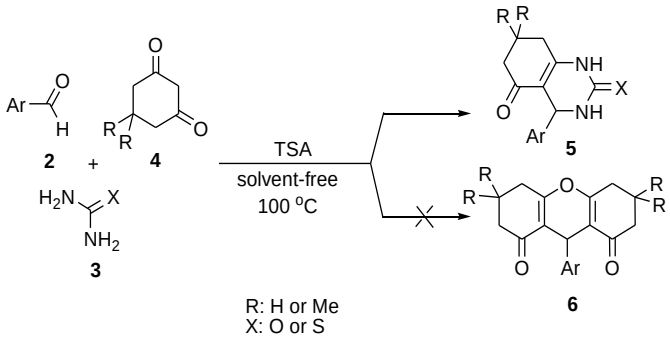


Figure 3. Recyclability of TSA in synthesis of 5a under optimized conditions. Reaction time: 50 min.



Scheme 2. Three-component condensation of aryl aldehydes, cyclic 1,3-dione, and urea / thiourea using TSA (1)

Table 2. Synthesis of 5 via the Biginelli method using TSA (1) at 100 °C under solvent-free conditions.

Entry	R	Ar	X	Time (min)	Yield (%)[a]	M.p. (°C)
5a	Me	C_6H_5	O	50	90	288-290
5b	Me	4-MeO-C_6H_4	O	60	80	272-274
5c	Me	2-Cl- C_6H_4	O	60	85	271-273
5d	Me	4-Br- C_6H_4	O	30	80	324-326
5f	Me	4-F- C_6H_4	O	40	78	300-302
5g	Me	2-MeO- C_6H_4	O	25	85	197-199
5h	Me	4-Me-C_6H_4	O	30	90	300-302
5i	Me	3-O_2N- C_6H_4	O	25	90	297-299
5j	H	C_6H_5	O	45	90	275-277
5k	H	4-Cl-3-O_2N- C_6H_3	O	30	85	209-211
5l	H	4-Br- C_6H_4	O	35	80	275-277
5m	H	4-Cl- C_6H_4	O	30	85	281-282
5n	H	2-MeO- C_6H_4	O	25	80	197-199
5o	Me	2,4-Cl_2- C_6H_3	O	25	85	263-265
5p	Me	3-Br-C_6H_4	O	30	90	265-267
5q	Me	3-Cl-C_6H_4	O	45	80	290-292
5r	Me	4-Me-C_6H_4	S	40	85	280-282
5s	Me	4-Br-C_6H_4	S	60	75	290-292
5t	Me	4-MeO-C_6H_4	S	65	80	268-270
5u	Me	C_6H_5	S	65	80	280-282

4. Conclusions

To conclude, this simple catalytic system is remarkably tolerant to a variety of functional groups on the aryl aldehyde and offers significant advantages such as, low catalyst loading, high yields, avoidance of organic solvents, the use of a safe and recyclable catalyst, short reaction times, and operational simplicity. Therefore, based this comment, the current protocol is economic and environmentally friendly.

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