An Efficient and Clean One-pot Synthesis of 3,4-Dihydropyrimidine-2(1*H*)-ones Catalyzed by Tungstate Sulfuric Acid in Solvent-free Conditions

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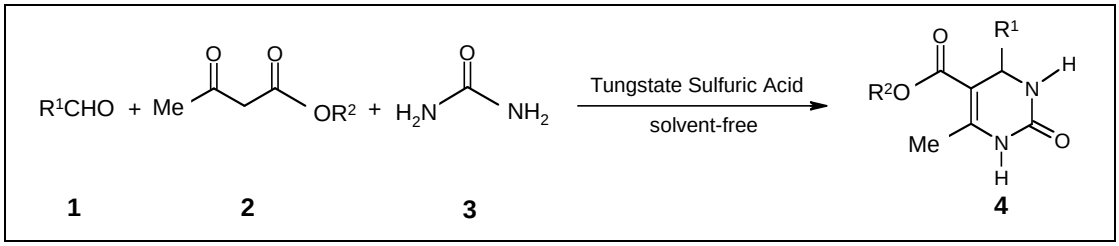

Tungstate sulfuric acid catalyzes the three component condensation reaction of an aromatic aldehyde, urea and a β-ketoester under solvent-free conditions to afford the corresponding dihydropyrimidinones in high to excellent yields at room temperature.

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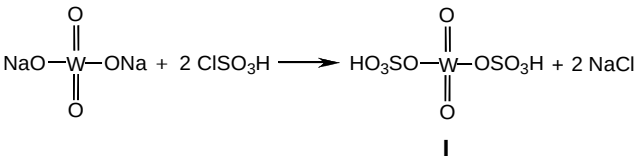
INTRODUCTION

Dihydropyrimidinones belong to an important class of heterocyclic compounds that have attracted organic chemists due to pharmacological and biological properties, such as antihypertensive activity, calcium channel blocking, alpha-1a-antagonism, neuropeptide Y(NPY) antagonism, antitumor, antibacterial, and anti-inflammatory activity [1–4]. Recently, the batzelladine alkaloids containing the dihydropyrimidin-one-5-carboxylate core have been found to be potent HIV-gp-120-CD4 inhibitors [5]. Due to the importance of these compounds as synthons in organic synthesis, many synthetic methods for preparing such compounds have been developed based on the Biginelli reaction [6]. However, there are several disadvantages associated with the reported methodologies including unsatisfactory yields, long conversion times, difficult handling of reagents, toxic and inflammable organic solvents, and incompatibility with other functional groups in the molecules that limit these methods to small-scale synthesis. Thus, developments of facile and environmentally friendly synthetic methods for preparation of the dihydropyrimidinones are yet demanded. Also in view of the pharmaceutical importance of these compounds, many improved catalytic methods have been developed [7-11].

It is well known in the protocol of green chemistry that its main objective is to perform reactions under solventless conditions using heterogeneous catalysts, in order to generate environmentally friendly chemical transformations [12]. In addition, it is important to note that an ideal synthesis is considered as one in which a target molecule is produced quantitatively in one step, from available and inexpensive raw materials, under environmentally harmless processes [13].

Today, substitution of homogenous reagents or catalysts by heterogeneous ones is an active field both in chemical industries and in laboratorial synthetic methods. This is due to some advantages such as simplification in handling, reduction of corrosion, green chemistry point of view, avoidance of byproducts, easy and clean reaction and simple work-up. Regarding the wide application of acids as reagents or catalysts in organic chemistry, preparation of a new inorganic solid acid can be useful in this direction. Recently silica sulfuric acid and Nafion-H® [14] have been used for a wide variety of reactions [15]. In continuation of above and our studies [16] on the application of inorganic solid acid, we found that anhydrous sodium tungstate reacts with chlorosulfonic acid (1:2 mole ratio) to give tungstate sulfuric acid **I**. The reaction is performed easy, clean and without any work-up (Scheme 1). It is to be noted that there is no gas production during the reaction.

Scheme 1

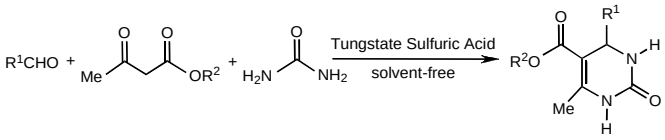


In continuation of our programme on utility of tungstate sulfuric acid (**I**) in organic reactions, herein we were interested to examine it as proton source in the synthesis of dihydropyrimidinones.

RESULTS AND DISCUSSION

In this work [17], we wish to report an efficient and convenient procedure for the synthesis of dihydropyrimidinones from the alkyl or aryl aldehydes using tungstate sulfuric acid as catalyst (Scheme 2).

Scheme 2



Two parallel reaction series, one according to classical Biginelli reaction (method B) and another in our conditions (method A) were designed. As shown in Table 1, the product yields were low (29-76%) after 18 h, when the reactions were carried out with HCl (aq.) alone (as classical Biginelli reaction) whereas the same reactions in the presence of tungstate sulfuric acid gave high to excellent yields (89-97%) after 5-20 minutes under solvent free conditions.

We extended these reaction conditions to a series of alkyl or aryl aldehydes under solvent free conditions. Both aromatic aldehydes bearing either activating or deactivating groups reacted well with β- ketoesters to yield the corresponding dihydropyrimidinones in high to excellent yields (Entries 1-23). It is noteworthy that acid-sensitive substrates such as cinnamaldehyde also proceeded well to give the dihydropyrimidinones without any side products (Entry 17). However, aliphatic aldehydes such as butanal as observed previously are quite resistant to our reaction conditions [7d].

To use of tungstate sulfuric acid in large-scale synthesis especially in chemical laboratory, a typical reaction was performed for synthesis of **4j** with ten fold amounts of reactants and catalyst with respect to one mentioned in the experimental section. The result showed that the yield of 91% in these conditions is comparable with that one in Table 1.

To achieve the reaction efficiency of recovered catalyst, the reaction mixture of **4j** was treated by hot ethanol for 5 minutes and then filtered and washed with hot ethanol twice to give tungstate sulfuric acid. The recovered acid was used again for synthesis of **4j** that lead to the yield of 85%.

In conclusion, we have found an efficient, inexpensive reagent and straightforward procedure for one-pot synthesis of dihydropyrimidinones using tungstate sulfuric acid as catalyst. Also it was found that the performance of the catalytic system is greatly facilitated when used without solvents, important from the view-point of green chemistry. Moreover, nonhygroscopic and inexpensive for this transformation are other advantages of this procedure.

Table 1

Synthesis of dihydropyrimidinones catalyzed with tungstate sulfuric acid under solvent-free conditions.

Entry	DHPM	R^1	R^2	Yield(%)[a]		Mp (°C)	
				A[b]	B[c]	Found	Reported
1	**4a**	C_6H_5	Me	96	40	210-211	209-211[6c]
2	**4b**	4-Cl-C_6H_4	Me	95	57	205-207	206-208[6c]
3	**4c**	4-CH_3-C_6H_4	Me	96	-	201-202	203[6a]
4	**4d**	3,4-$(CH_3O)_2$-C_6H_3	Me	90	-	150-153	150-152[6d]
5	**4e**	4-OH-3-CH_3O-C_6H_3	Me	89	-	221-222	220-222[6d]
6	**4f**	4-CH_3O-C_6H_4	Me	94	29	193-194	192-194[6c]
7	**4g**	4-NO_2-C_6H_4	Me	92	44	235-237	236-237[6c]
8	**4h**	4-F-C_6H_4	Me	90	-	193-194	192-194[6f]
9	**4i**	2,4-$(Cl)_2$-C_6H_3	Me	94	-	252-254	254-255[6f]
10	**4j**	C_6H_5-	Et	97	76	201-203	202-203[6c]
11	**4k**	4-Cl-C_6H_4	Et	94	56	214-216	215-216[6c]
12	**4l**	4-CH_3-C_6H_4	Et	95	-	170-171	170[6e]
13	**4m**	3,4-$(CH_3O)_2$-C_6H_3	Et	93	-	176-178	176-177[6e]
14	**4n**	4-OH-3-CH_3O-C_6H_3	Et	90	43	232-233	231-232[6c]
15	**4o**	4-CH_3O-C_6H_4	Et	95	60	202-203	201-202[6c]
16	**4p**	4-NO_2-C_6H_4	Et	91	58	207-208	208-209[6c]
17	**4x**	C_6H_5-CH=CH	Et	90	-	231-234	232-235[6f]
18	**4r**	3-NO_2-C_6H_4	Et	92	49	226-227	227-228[6c]
19	**4s**	2,4-$(Cl)_2$-C_6H_3	Et	95	69	247-249	248-250[6b]
20	**4t**	4-F-C_6H_4	Et	92	-	184-186	185-186[6g]
21	**4u**	3-OH-C_6H_4	Et	94	-	165-167	164-166[6h]
22	**4v**	4-Br-C_6H_4	Et	92	-	195-198	197[6e]
23	**4w**	4-$N(CH_3)_2$-C_6H_4	Et	93	-	255-257	256-258[6b]
24	**4q**	$CH_3(CH_2)_2$	Et	25	15	153-155	152-154[6b]

[a] Isolated yields; [b] Method A: new reaction conditions in solvent-free (cat. tungstate sulfuric acid, 5-20 min); [c]Method B: classical Biginelli conditions (cat. HCl in EtOH, reflux 18h).

EXPERIMENTAL

All chemicals were purchased from Merck, Fluka and Sigma-Aldrich chemical companies. The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with authentic samples. IR spectra were recorded on FT-IR JASCO-680, the ^{1}H-NMR spectra were obtained on a Brüker-instrument DPX-300 MHz and melting points were determined on a Barnstead Electrothermal (BI 9300) apparatus.

Preparation of tungstate sulfuric acid (I). Anhydrous sodium tungstate was prepared by drying of sodium tungstate dihydrate (Na_2WO_4. $2H_2O$, MW = 329.86) in the oven at 200°C for 4 hours. To 0.2 mol of chlorosulfonic acid (23.30 g, 13.31 mL) in 250 mL round bottom flask in the ice-bath, 0.1 mol (29.38 g) anhydrous sodium tungstate was added gradually with stirring. After the completion of addition of anhydrous sodium tungstate, the reaction mixture was shaken for 1 h. Then 50 mL of cold water was added to the reaction mixture and stirred for 10 minutes. The mixture was filtered and a yellowish-white solid of tungstate sulfuric acid, 40.2 g (98%), m.p. 285°C (dec.) was obtained. Characterstic IR bands (KBr, cm^{-1}): 3600-2200 (OH, bs), 1240-1140 (S=O, bs), 1060 (S-O, m), 1005 (S-O,m), 880-840 (W=O, m), 450 (W-O, m) [16].

Typical procedure for the preparation of 5-(Ethoxy-carbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4j). A mixture of benzaldehyde (1 mmol), ethyl-acetoacetate (1 mmol), urea (1.5 mmol) and tungstate sulfuric acid (1 mmol) in a mortar was prepared. The mixture was ground with a pestle for 10 minutes. After completion of the reaction as monitored by TLC, 5 mL of ethanol was added to the reaction mixture, stirred and heated for 5 minutes. The reaction mixture was filtered and washed with hot ethanol. The hot filtrate was poured onto crushed ice, the solid product collected by filtration and washed with cold ethanol and a mixture of ethanol-water. The solid product was recrystalized from ethanol. The products were characterized by IR, ^{1}H-NMR and *via* comparison of their melting points with the reported ones.

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrim-idin-2(1*H*)-one (4j). IR (KBr), ν (cm^{-1}): 3232, 3104, 2936, 1718, 1696, 1598, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ (ppm): 8.15 (1H, s), 7.1-7.35 (5H, m), 6.15 (1H, s), 5.42 (1H, s), 4.10 (2H, q), 2.34 (3H, s), 1.25 (3H, t); MP = 201-203 ° C (Lit. [6c] 202-203 ° C)

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