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Note

$VOSO_4$-catalyzed Biginelli condensation: An efficient synthesis of dihydro-1*H*-pyrimidine-2-thione/one and octahydro-2,5-quinazolinedione

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The three component condensation of an aldehyde **1**, urea/thiourea **2** and *β*-ketoester **3** / dimidone **7** in the presence of a catalytic amount of $VOSO_4$ is disclosed for the synthesis of 3,4-dihydro-1*H*-pyrimidine-2-thione/one (DHPMs) **4** and octahydro-2,5-quinazolinedione **8** under solvent-free microwave irradiation conditions. High yields are achieved even on 1 g scale, while reaction times are considerably shortened compared to conventional heating conditions.

Keywords: $VOSO_4$ catalyst, dihydro-1*H*-pyrimidine-2-thione/one, octahydro-2,5-quinazolinedione, solvent-free, microwave irradiation

Development of a simple, safe, ecofriendly and economic synthetic routes for widely used organic compounds from the readily available reagents are one of the major challenges in organic synthesis. 3,4-Dihydro-1*H*-pyrimidine-2-one esters (DHPMs) are among such type of organic compounds which belong to an important class with significant therapeutic and medicinal properties[1], some of which have antiviral, antitumor, antibacterial and anti-inflammatory activity[2-6]. Several marine alkaloids having the DHPM core unit are showing interesting biological activities[7] such as calcium channel blockers[8], antihypertensive agents[9] and *α*-1a-adrenoreceptor antagonists[10]. The structurally rather simple DHPM monastrol (**Figure 1**) specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs[11]. The batzelladine alkaloids (**Figure 1**) containing the DHPM core unit inhibit the binding of HIV envelope protein gp-120 to human CD_4 cells and, therefore, are potential new leads for AIDS therapy[12]. Therefore, the synthesis of compounds with DHPMs core unit has gained much importance. Although many synthetic methods have been developed[13-16], most of these methods suffer from one or the other disadvantages such as long reaction times, harsh reaction conditions, and the use of stoichiometric reagents or of toxic and inflammable solvents, difficult work-ups or low yields of products. Hence, it is desirable to develop an easy, safe and economical procedure, avoiding strong acids, hazardous or expensive reagents and other corrosive media. In this regard vanadium (IV) is used as a catalyst for the synthesis of DHPMs as it participates as a catalyst in important biological processes[17], and also has been used as a catalyst for organic reactions such as coupling reactions[18], oxidation of sulphides[19], cyclooctene[20] and sugars[21], epoxidation of cyclohexene, stabilization of endiolates[22] and other reactions[23-27].

In continuation of our interest to develop new methodologies in organic reactions[28], in this communication, a simple and effective Biginelli reaction that produces high yields of DHPMs in a short reaction time is disclosed under solventless microwave irradiation using a catalytic amount of $VOSO_4$, while preserving the original one-pot strategy.

In order to explore the catalytic activity of $VOSO_4$ and also the effect of microwave irradiation of the Biginelli reaction, a mixture of benzaldehyde, ethyl acetoacetate, urea (1.1:1.0:2.0 molar ratio) and a catalytic amount of $VOSO_4$ was irradiated under solventless microwave irradiation conditions at 360 W for 3 min, which gave **4a** in an excellent yield. Under similar conditions, different substituted aldehydes were converted to their corresponding DHPMs (**Scheme I**) in good yields and the results are summarized in **Table I**.

The important features of microwave/$VOSO_4$ mediated Biginelli protocol are: In many cases the product obtained is at least 95% purity, high yields, survival of a variety of functional groups such as methoxy **4b**, **4g** and **4j**, halide **4c** and nitro **4e**. In fact, the aliphatic **4m** and **4n** aldehydes also gave excellent yields. It is presumed that the reaction may proceed through the imine intermediate **5,** formed from the aldehyde and urea/thiourea and stabilized by the vanadium ion, followed by the addition of enolate of *β*-ketoester **3** and cyclodehydration of **6** to afford the DHPMs (**Scheme II**).

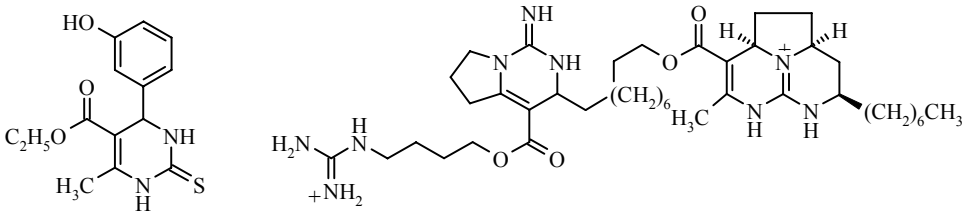
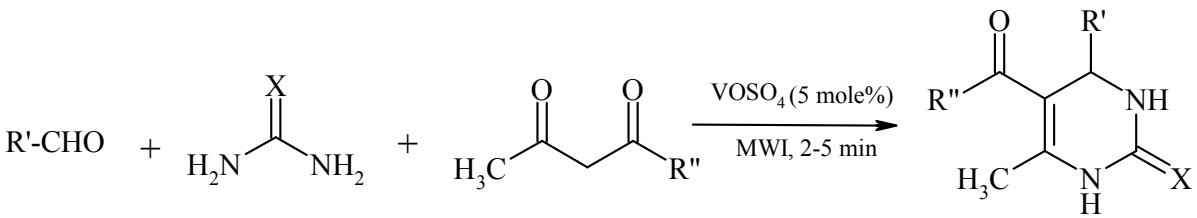
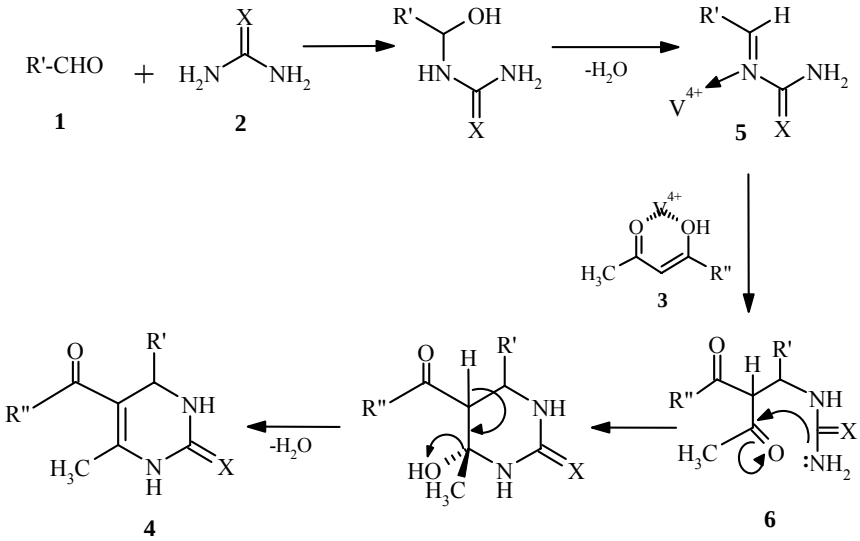


Figure 1 — Examples of biologically active DHPMs



Scheme I



Scheme II

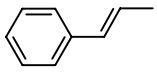
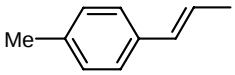
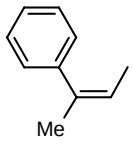
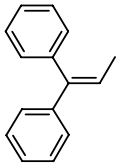
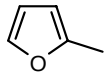
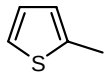
This reaction was further explored for the synthesis of octahydro-2,5-quinazolinedione **8** by the reaction of aldhyde **1** urea **2** and dimidone **7** under similar reaction conditions, compound **8** was obtained in excellent yields (**Scheme III**).

In conclusion, a simple, in-expensive, efficient and solvent-free microwave induced method for the Biginelli condensation using $VOSO_4$ catalyst has been developed. The advantages of this environmentally benign and safe protocol include a simple reaction setup, high yields, shorter reaction times, simple work-up and also have the ability to tolerate a wide variety of substituents in all the three components, which makes it a useful process for the synthesis of DHPMs.

Experimental Section

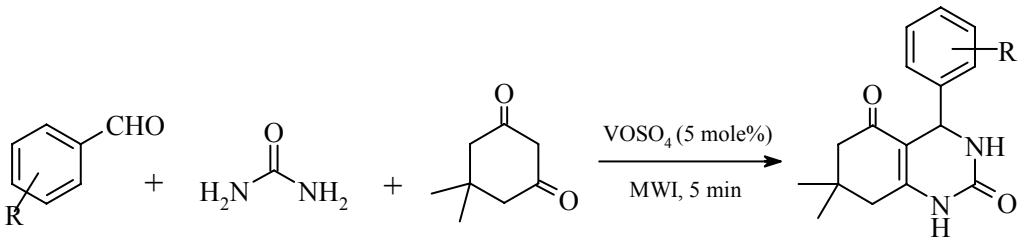
Melting points were uncorrected and were determined in open glass capillaries on Fisher-Johns apparatus. IR spectra (KBr) were recorded on a

Table I—$VOSO_4$ catalyzed synthesis of dihydropyrimidinones and dihydropyrimidinethione **4a-t** under solvent-free conditions

DHPMs[a]	R'	R''	X	Reaction time (min)	Yield (%)[b]
4a	C_6H_5-	OEt	O	3	96
4b	4(MeO)C_6H_4-	OEt	O	3	98
4c	4-Cl-C_6H_4-	OEt	O	5	83
4d	4-Me-C_6H_4-	OEt	O	4	90
4e	4-(NO_2)-C_6H_4-	OEt	O	5	90
4f	4-(NMe_2)-C_6H_4-	OEt	O	5	86
4g	3,4-di-MeO-C_6H_3-	OEt	O	4	89
4h	3,4-(OCH_2O)-C_6H_3	OEt	O	4	90
4i	C_6H_5-	OMe	O	2	94
4j	4-(MeO)-C_6H_4-	OMe	O	2	93
4k	4-Me-C_6H_4-	OEt	S	3	92
4l	C_6H_5-	OEt	S	2	87
4m	CH_3-CH_2-	OEt	O	2	90
4n	CH_3-CH_2-	OEt	S	2	91
4o		OEt	O	4	94
4p		OEt	O	4	91
4q		OEt	O	5	89
4r		OEt	O	5	86
4s		OEt	O	5	84
4t		OEt	O	4	96

[a]All the products were characterized by IR, ^{1}H NMR, MS and elemental analyses.
[b]The yields refer to the isolated products.

Perkin-Elmer spectrum BX series FT-IR spectrometer. ^{1}H NMR spectra were obtained on a Verian Gemini (300 MHz) spectrometer. TMS was used as an internal standard and $CDCl_3$/DMSO-d_6 as the solvent. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. $VOSO_4$ is procured from Aldrich chemical company. All the aldehydes, β-ketoesters, dimidone and urea/thiourea



1 **2** **7** **8a,b**

Scheme III

are commercially available. For the microwave irradiation, a conventional house hold microwave oven was used.

Synthesis of ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidine carboxylate 4a: A mixture of benzaldehyde **1** (1.11 mL, 0.01 mole), urea **2** (1.2 g, 0.02 mole) and β-ketoester **3** (1.45 mL, 0.011 mole) was mixed with $VOSO_4$ (11 mg, 5 mole %) in a glass tube and placed the tube at the center of an alumina-bath, kept inside a microwave oven and the mixture was irradiated at 360W microwave power for the specified time (**Table I**). On completion of the reaction, indicated by TLC, the mixture was cooled and quenched with water. The solid separated was filtered and recrystallized from ethanol to afford pure, DHPMs **4** in good yields. The other compounds **4b-t** were prepared by similar procedure.

Ethyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate 4g: m.p. 182-84°C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 9.16 (s, 1H), 7.51 (s, 1H), 6.84 (d, 1H, J = 8.1 Hz), 6.90 (s, 1H), 6.62 (d, 1H, J = 8.1 H), 5.22 (d, 1H, J = 3.4 Hz), 4.04 (q, 2H), 3.67 (s, 6H), 2.28 (s, 3H), 1.12 (t, 3H); IR (KBr): 3350, 3236, 2965, 1720, 1645, 1220 cm^{-1}; Mass: *m/z* 320 (M^+). Anal. Calcd. for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.71; H, 6.32; N, 8.69%.

Ethyl-6-methyl-4-[(*E*)-2-(4-methylphenyl)-1-ethenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate 4p: m.p. 226-28°C; ^{1}H NMR ($CDCl_3$+ DMSO-d_6): δ 9.92 (s, 1H), 9.72 (s, 1H), 7.46 (d, 2H, J = 7.8 Hz), 7.11 (d, 2H, J = 7.8 Hz), 6.71 (d, 1H, J = 15.7 Hz), 6.36 (dd, 1H, J = 15.7, 5.2), 4.82 (d, 1H, J = 5.2 Hz), 4.02 (q, 2H), 2.38 (s, 3H), 2.22 (s, 3H), 1.09 (t, 3H); IR (KBr): 3345, 3238, 2945, 1720, 1645, 1600, 1224 cm^{-1}; Mass: *m/z* 300 (M^+). Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.82; H, 6.70; N, 9.22%.

Ethyl-6-methyl-2-oxo-4-[(*E*)-2-phenyl-1-propenyl]-1,2,3,4-tetrahydro-5-pyrimidine carboxylate 4q: m.p. 189-91°C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 9.92 (s, 1H), 9.74 (s, 1H), 7.00-7.40 (m, 5H), 6.01 (d, 1H, J = 5.62 Hz), 4.80 (d, 1H, J = 5.62 Hz), 4.05 (q, 2H), 2.32 (s, 3H), 2.02 (s, 3H), 1.10 (t, 3H); IR (KBr): 3340, 3252, 2965, 1720, 1644, 1595, 1226 cm^{-1}; Mass: *m/z* 300 (M^+). Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.81; H, 6.59; N, 9.17%.

Ethyl-4-(2,2-diphenylvinyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate 4r: m.p. 238-40°C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 9.91 (s, 1H), 9.57 (s, 1H), 7.47-7.82 (m, 10H), 6.47 (d, 1H, J = 5.52 Hz), 4.51 (d, 1H, J = 5.52 Hz), 3.99 (q, 2H), 2.32 (s, 3H), 1.10 (t, 3H); IR (KBr): 3320, 3245, 2961, 1720, 1640, 1596, 1226 cm^{-1}; Mass: *m/z* 362 (M^+). Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.83; H, 6.02; N, 7.66%.

The other products reported in **Table I** are known compounds for which satisfactory spectroscopic data were obtained.

General procedure for the synthesis of octahydro-2,5-quinazolinedione 8: A mixture of benzaldehyde/4-methoxybenzaldehyde **1** (1.11 mL/1.47 mL, 0.01 mole), urea **2** (1.2 g, 0.02 mole) and dimidone **7** (1.68 g, 0.012 mole) was mixed with $VOSO_4$ (11 mg, 5 mole%) in a glass tube and irradiated in a microwave oven at 360 W for 5 min. On completion of the reaction, indicated by TLC, the mixture was cooled and quenched with water. The solid separated was filtered and recrystallized from ethanol to afford pure **8** in good yields.

7,7-Dimethyl-4-phenyl-1,2,3,4,5,6,7,8-octahydro-2,5-quinazolinedione 8a: m.p. 166-68°C; ^{1}H NMR (DMSO-d_6): δ 7.12-7.39 (m, 5H), 6.24 (s, 1H), 5.96 (d, 1H, J = 5.2 Hz), 5.29 (s, 1H), 2.48-2.62 (m, 4H), 1.1 (s, 6H); IR (KBr): 3347, 3068, 1682, 1610 cm^{-1}; Mass: *m/z* 270 (M^+). Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.12; H, 6.82; N, 10.17%.

4-(4-Methoxyphenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-2,5-quinazolinedione 8b: m.p. 142-44°C;

^{1}H NMR (DMSO-d_6): δ 6.98 (d, 2H, J = 8.44 Hz), 6.86 (d, 2H, J = 8.44 Hz), 6.23 (s, 1H), 5.87 (d, 1H, J = 5.2 Hz), 5.42 (s, 1H), 3.82 (s, 3H), 2.48-2.62 (m, 4H), 1.0 (s, 6H); IR (KBr): 3400, 3069, 1682, 1595, 1270 cm^{-1}; Mass: *m/z* 300 (M^+). Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.81; H, 6.83; N, 9.26%.

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