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An ultrasonic assisted multicomponent reaction for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones under solvent-free condition

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ABSTRACT

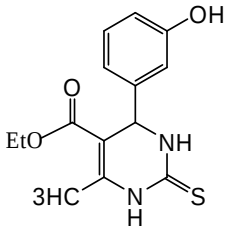
An efficient sonochemistry methodology is described for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones (Biginelli reaction) by condensation of various substituted benzaldehydes, Diketone/ β-ketoester and urea/ thiourea, at ambient temperature promoted by Chlorosulphonic acid ($ClSO_3H$) under solvent-free condition. This method gives the desired dihydropyrimidines in excellent yields in short reaction time at ambient temperature.

Keywords: Biginelli reaction; Chlorosulphonic acid catalyst; Solvent-free condition; Sonochemistry.

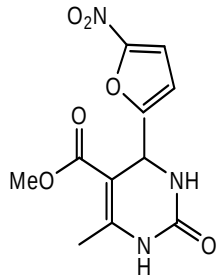
INTRODUCTION

In recent years, 3, 4-dihydropyrimidin-2-(1H)-ones (DHPMs) and their derivatives have attracted considerable interest because of their therapeutic and pharmacological properties.[1] Several of them have been found to exhibit a wide spectrum of biological effects[2] including antiviral, antitumor, antibacterial and anti-inflammatory activities. In addition 4-aryl dihydropyrimidine ones have emerged as potent calcium channel blockers, antihypertensive, α1a-adrenergic antagonists and neuro peptides antagonists [3]. For example dihydropyrimidines 2, 3,4, were shown to have antiviral, calcium channel blocking and antihypertensive activity[4], and DHPMs 5a and 5b (derivatives of 4-(3-hydroxyphenyl)-2- thiones) and Monastrol 1, which has excellent anticancer activity[5] as cell permeable lead compounds for the development of new anticancer

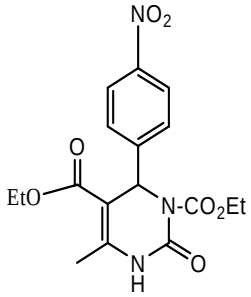
drugs, that specifically affects cell division (mitosis). Moreover several alkaloids containing the DHPM unit have been isolated from marine natural sources including batzelladine alkaloids, which also exhibit interesting biological properties [6], (found to be potent-HIV gb-120-CD_4 inhibitors) [7].



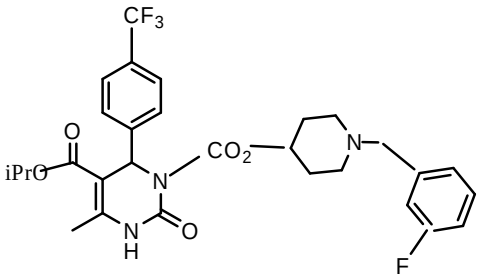
1
Monastrol



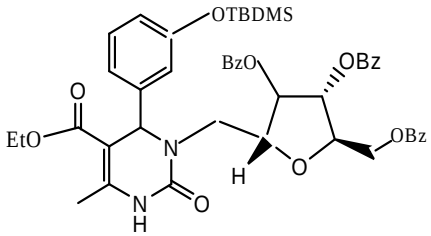
2
Antiviral



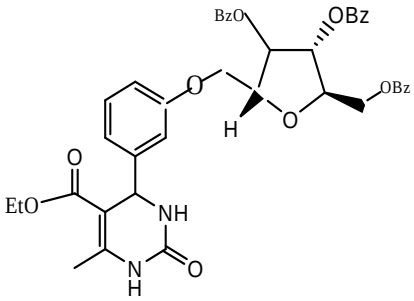
3
calcium channel blocker



4
Antihypertensive



5a



5b

The synthesis of this important heterocyclic nucleus was reported by Biginelli in 1893, it is acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde, and urea [8]. The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling, the reaction mixture was identified as 3,4-dihydropyrimidin-2(1H)-one[9]. However, one serious drawback of the Biginelli reaction is low yields in the case of substituted aromatic and aliphatic aldehydes[10].This has led to the development of multistep strategies resulting in marginally improved yields[11].While the early examples of this cyclocondensation process typically involved a β-ketoester, aromatic aldehyde and urea, the scope of this heterocycle synthesis has now been extended considerably by

variation of all three building blocks, allowing access to a large number of multifunctionalized pyrimidine derivatives[12]. These multistep methods lack the simplicity of the one-pot, one-step procedure. So the Biginelli reaction for the synthesis of DHPMs has attracted renewed attention and many improved procedures have been reported. Many of these procedures employ catalysts such as ($BF_3 \cdot OEt_2$),[13] polyphosphate ester[14], montmorillonite KSF[15], zeolites[16], ($FeCl_3 \cdot 6H_2O$)[17], ($LaCl_3 \cdot 7H_2O$)[18], ($Yb(OTf)_3$)[19], ($InCl_3$)[20]. In addition methods employing microwave [21], ultrasound [22], solid and fluorousphase syntheses [23] have been reported. Most of the methods reported above use expensive catalysts, strong acidic conditions, and higher temperatures and require longer reaction times. Some of the methods resulted in unsatisfactory yields and involved cumbersome product isolation procedures. The standard procedure consist either of stirring the reactants for 2-3 days at room temperature,[24] or simple refluxing the reactants for 3-4h.[25] Therefore the development of new methods at moderate temperature, milder reaction conditions, short reaction times and better yields can possibly would extend the scope of the Biginelli reaction. Upon microwave irradiation of the reaction mixture, the reaction time can be dramatically shortened to a few minutes [26]. For many years ultrasound has found a variety of uses in engineering, science and medicine. However, its application to chemistry (Sonochemistry) has received attention only in the recent past.[27,28] The interaction of acoustic waves with a chemical system is not merely an improved way of achieving agitation or surface cleaning, as it involves complex physico-chemical phenomena which are currently a matter of advanced research[29]. The effect of ultrasound has mostly been shown by increasing the yields of reactions and in some cases the ratio of formed products. The most important effect of ultrasound is by passing its waves through a liquid medium in the generation of energy [30]. The driving energy is provided by cavitations, the formation and collapse of bubbles, which liberates considerable energy in very short times [31].

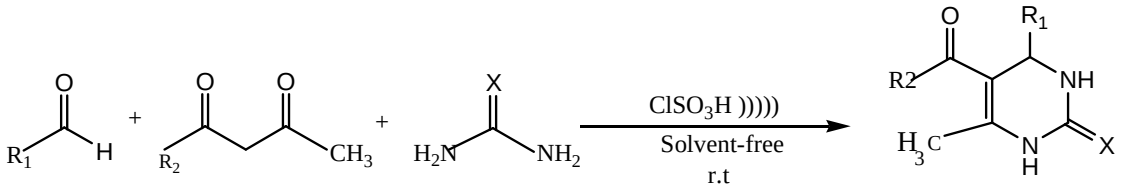
EXPERIMENTAL SECTION

All melting points were measured in open capillaries and are uncorrected. Silica gel used for TLC was 200-300 mesh with Binder. IR spectra were recorded on a SHIMADZU instruments. Proton magnetic Resonance Spectra were recorded on a Varian T-60, FT 80 A MSL-300 instrument. All spectra were recorded in $CDCl_3$and chemical shifts are reported in parts per million (ppm) down field from tetra methyl silane (TMS) as the internal standard. For ultrasound assisted organic reactions, ultrasonicator was used. The technical specifications are as follows:
Electric supply: 230 v A.C. 50 Hz, 1phase.
Ultrasonic frequency: 36 ±3 KHz.
Ultrasonic power: 100 watts.

General procedure:
A mixture of 1,3_dicarbonylcompound (10 mmol), aldehyde (10 mmol), urea/thiourea (15 mmol) and 0.2 mmol of chlorosulfonic acid was added slowly and irradiated by sonicator at ambient temperature. After completion of reaction, monitored by TLC, the reaction mixture was poured into ice water and the precipitated solid was collected by filtration, washed with water and dried. The crude product obtained was recrystallised from ethanol to give pure compound as white solid. All compounds obtained according to this protocol were characterized and identified by their melting points and spectral date in comparison to those reported in the literature. The results are summarized in (Table 1).

RESULTS AND DISCUSSION

We report here the application of the ultrasound induced Biginelli condensation for 3,4-dihydropyrimidin-2(1H)-ones and thiones, catalyzed by Chlorosulfonic acid under solvent-free conditions. The one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under ultrasound activation involves the condensation of aromatic aldehydes, Diketone/β- ketoester and urea /thiourea (Scheme 1).



R1=Ar
R2=OEt,Me
X=O,S

Scheme 1

The process was promoted by directly immersing of reaction vessels into the ultrasonic cleaning bath which provides a fairly even distribution of energy into the reaction medium. The reaction was completed within 5-30 minutes, as compared to 30-60 minutes under thermal conditions, [25] with a substantial increase in the yield of product. The results are summarized in Table 1. This is an efficient and environmentally benign methodology for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones at ambient temperature. Work of the reaction is easy and products are obtained in excellent yields.

Table 1: Chlorosulfonic acid catalyzed highly efficient solvent free synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones and thiones under ultrasound irradiation

Entry	R1	R2	X	Time in minutes	Yield (%)	M.P (Obs./literature)^{0}C	
						Observed	Reported
1	C_6H_5	C_2H_5O	O	5	96	202-203	(201-203)[19]
2	4-Cl-C_6H_4	C_2H_5O	O	10	94	213-214	(210-212) [19]
3	2-Cl-C_6H_4	C_2H_5O	O	15	92	222-223	(215-218) [2]
4	4-OMe-C_6H_4	C_2H_5O	O	10	93	201-203	(199-201) [19]
5	2-OH-C_6H_4	C_2H_5O	O	15	85	200-202	(200-202) [33]
6	C_6H_5CH=CH	C_2H_5O	O	10	75	228-230	(232-234) [34]
7	C_6H_5	C_2H_5O	S	20	93	208-210	(205-207) [19]
8	4-Cl-C_6H_4	C_2H_5O	S	15	90	182-184	(180-182) [35]
9	4-OMe-C_6H_4	C_2H_5O	S	30	92	150-152	(150-152) [36]
10	2-OH-C_6H_4	C_2H_5O	S	25	81	188-190	(183-185) [37]
11	2-NO_2- C_6H_4	C_2H_5O	O	15	83	210-211	(206-208) [38]
12	C_6H_5	CH_3	O	10	94	240-242	(233-236) [19]
13	C_6H_5	CH_3	S	15	87	220-222	(220-222) [39]
14	4-Cl-C_6H_4	CH_3	O	15	91	207-209	(204-209) [40]

Physical and Spectral data for all the compounds:

Ethyl6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridimidine-5 carboxyl- ate(1). ^{1}H NMR ($CDCl_3$): δ (ppm) =8.33 (s, 1H, NH), 5.87 (s, 1H, NH), 7.26-7.30 (m, 5H, C_6H_5), 5.39 (s, 1H, CH), 4.06 (q, J=6.88 Hz, 2H, OCH_2CH_3), 2.32 (s, 3H, CH_3), 1.15(t, J=6.88 Hz, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3242, 3117, 2980, 1722, 1645, 1600, 1462, 1388, 1091, 781; Anal. Calcd for $C_{15}H_{19}N_2O_3$: C, 65.44; H, 6.96; N, 10.17% Found: C, 65.42; H, 6.93; N, 10.20%.

Ethyl6-methyl-2-oxo-4(4-chlorophenyl)1,2,3,4-tetrahydropyridimidine-5- carboxylate(2).
^{1}H NMR ($CDCl_3$): δ(ppm) = 8.11(s, 1H, NH), 5.86(s, 1H, NH),7.23-7.29(m, 4H, C_6H_4), 5.37(s, 1H, CH), 4.07(q, J=7.15 Hz, 2H, OCH_2CH_3), 2.33(s, 3H, CH_3), 1.16(t, J=7.15Hz, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3246, 3111, 2982, 1708, 1645, 1575, 1464, 1321, 840, 783; Anal. Calcd for $C_{15}H_{18}ClN_2O_3$: C, 58.16; H, 5.86; N, 9.04% Found: C, 58.19; H, 5.81; N, 9.02%.

Ethyl6-methyl-2-oxo-4(2-chlorophenyl)-1,2,3,4-tetrahydropyridimidine-5- carboxylate(3)
^{1}HNMR($CDCl_3$): δ(ppm)=8.11(s, 1H, NH), 5.86(s, 1H, NH),7.26(m, 4H, C_6H_4), 5.37(d, J=2.20Hz, 1H, CH), 4.07(q, J=7.15Hz, 2H, OCH_2CH_3), 2.33(s, 3H, CH_3), 1.16(t, J=7.15Hz, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3234, 3117, 2982, 1707, 1647, 1575, 1462, 1319, 839, 783; Anal. Calcd for $C_{15}H_{18}ClN_2O_3$: C, 58.16; H, 5.86; N, 9.04% Found: C, 58.14; H, 5.82; N, 9.07%.

Ethyl6-methyl-2-oxo-4(4-methoxyphenyl)1,2,3,4-tetrahydropyridimidine-5- carboxylate(4).
^{1}HNMR($CDCl_3$): δ(ppm)=8.49(s, 1H, NH), 5.86(s, 1H, NH), 7.23 (d, J=8.53Hz, 2H, CHarom), 6.82(d, J=8.53Hz, 2H, CHarom), 5.33(s, 1H, CH), 4.06(q, J=6.88Hz, 2H, OCH_2CH_3), 3.77(s, 3H, OCH_3), 2.32(s, 3H, CH_3), 1.16(t, J=6.88Hz, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3238, 3113, 2980, 2835, 1707, 1649, 1510, 1460, 1282, 1176, 786; Anal. Calcd for $C_{16}H_{21}N_2O_4$: C, 62.93; H, 6.93; N, 9.17% Found: C, 62.89; H, 6.95; N, 9.22%.

Ethyl6-methyl-2-oxo-4(2-hydroxyphenyl)-1,2,3,4-tetrahydropyridimidine-5 carboxylate (5).
^{1}HNMR($CDCl_3$): δ(ppm)=7.26(d, J=4.67Hz, 1H, Ar-H), 7.21(s, 1H, NH), 6.93(d, J=7.43Hz, 2H, Ar-H), 6.84(t, J=8.25Hz, 1H, Ar-H), 5.66(s, 1H, NH), 4.62(d, J=8.25Hz, 1H, CH), 4.25(q, 2H, OCH_2CH_3), 3.14(s, 1H,OH), 1.88(s, 3H, CH_3), 1.30(t, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3348, 3244, 3082, 2989, 1687, 1504, 1462, 1232, 1087, 759; Anal. Calcd for $C_{15}H_{19}N_2O_4$: C, 61.84; H, 6.57; N, 9.62% Found: C, 62.88; H, 6.61; N, 9.64%.

Ethyl-6-methyl-2-oxo-4-cinnamyl-1,2,3,4–tetrahydropyrimidine5-carboxylate(6).
^{1}HNMR($CDCl_3$): δ(ppm)=7.30(m, 5H, C_6H_5), 7.07(s, 1H, NH, 6.50(d, J=15.4Hz, 1H, CH), 6.24(dd, J=15.4Hz, 1H, CH), 5.35(s, 1H, NH), 5.01(s, 1H, CH), 4.20(s, 2H, OCH_2CH_3), 2.32(s, 3H, CH_3), 1.21(t, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3240, 3109, 2976, 1703, 1653, 1460, 1226, 1093, 783; Anal. Calcd for $C_{18}H_{25}N_2O_3$: C, 68.11; H, 7.94; N, 8.83% Found: C, 68.18; H, 7.90; N, 8.80%.

Ethyl 6-methyl-2-thio-4-phenyl-1, 2, 3, 4-tetrahydropyridimidine-5-carboxylate(7).
^{1}HNMR($CDCl_3$): δ(ppm)= 7.71(s, 1H, NH), 7.32(m, 5H, C_6H_5), 7.12(s, 1H, NH), 5.40(d, J=2.48Hz, 1H, CH), 4.09(dq, J=7.4Hz, 2H, CH_2CH_3), 36(s, 3H, CH_3), 1.16(t, J=7.15Hz, 3H,

OCH_2CH_3); IR($CDCl_3$): (KBr) (ν_{max} cm-1) 3327, 3174, 3109, 2982, 1672, 1573, 1467, 1282, 1195, 1178, 1120, 761, 723, 692; Anal. Calcd for $C_{15}H_{19}N_2O_2S$: C, 61.83; H, 6.57; N, 9.61% Found: C, 61.79; H, 6.52; N, 9.63%.

Ethyl 6-methyl-2-thio-4(4-chlorophenyl)-1,2,3,4-tetrahydropyridimidine-5-carboxylate (8).
^{1}H NMR ($CDCl_3$): δ(ppm) =8.10(s, 1H, NH), 7.61(s, 1H, NH), 7.25(d, J=13.47Hz, 4H, C_6H_4), 5.37(s, 1H, CH), 4.09(d, J=5.22Hz, 2H, OCH_2CH_3), 2.36(s, 3H, CH_3), 1.19(d, J=4.68Hz, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3327, 3176, 3105, 2985, 1672, 1575, 1460, 1330, 1284, 1026, 754; Anal. Calcd for $C_{15}H_{18}ClN_2O_2S$: C, 55.29; H, 5.57; N, 8.60% Found: C, 55.33; H, 5.60; N, 8.65%.

Ethyl6-methyl-2-thio-4(4-methoxyphenyl)1,2,3,4-tetrahydropyridimidine-5- carboxylate(9).
^{1}HNMR($CDCl_3$): δ(ppm)=8.51(s, 1H, NH), 7.88(s, 1H, NH), 7.21(d, 2H, Ar-H), 6.83(d, 2H, Ar-H), 5.33(s, 1H, CH), 4.10(q, 2H, CH_2CH_3), 3.77(s, 3H, OCH_3), 2.34(s, 3H, CH_3), 1.19(t, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3313, 3171, 3105, 2989, 1668, 1575, 1460, 1373, 1332, 1259, 1192, 1118, 769; Anal. Calcd for $C_{16}H_{21}N_2O_3S$: C, 59.79; H, 6.59; N, 8.72% Found: C, 59.82; H, 6.56; N, 8.75%.

Ethyl6-methyl-2-thio-4(2-hydroxyphenyl)-1,2,3,4-tetrahydropyridimidine-5-carboxylate(10).
^{1}H NMR ($CDCl_3$): δ(ppm)=7.46(brs, 1H, NH), 7.12(d, J=7.42Hz, 1H, Ar-H), 6.94(s, 1H, NH), 6.94(t, J=7.42Hz, 2H, Ar-H), 6.85(d, J=7.97Hz, 1H, Ar- H), 4.71(d, J=2.47Hz, 1H, CH), 4.24(q, J=7.15Hz, 2H, OCH_2CH_3), 3.13(brs, 1H, OH), 1.91(s, 3H, CH_3),1.30(t, J=7.15Hz, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3363, 3171, 3082, 2993, 1728, 1560, 1485, 1329, 1153, 1091, 765; Anal. Calcd for $C_{15}H_{19}N_2O_3S$: C, 58.61; H, 6.23; N, 9.11% Found: C, 58.65; H, 6.27; N, 9.14%.

Ethyl6-methyl-2-oxo-4(2-nitrophenyl)-1,2,3,4-tetrahydropyridimidine-5-carboxylate(11).
^{1}HNMR($CDCl_3$): δ(ppm)=8.44(s, 1H, NH), 7.26-7.91(m, 4H, ArH), 6.03(s, 1H, NH), 5.81(d, J=2.48Hz, 1H, CH), 3.94(q, J=4.95Hz, 2H, OCH_2CH_3), 2.49(s, 3H,CH_3), 097(t, J=5.23Hz, 3H, OCH_2CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3477, 3294, 3147, 2991, 1668, 1600, 1525, 1450, 1371, 1134, 738; Anal. Calcd for $C_{15}H_{18}N_3O_5$: C, 56.24; H, 5.66; N, 13.12% Found: C, 56.28; H, 5.71; N, 13.14%.

5-Aceto6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridimidine(12).
^{1}H NMR ($CDCl_3$): δ(ppm)=7.32(m, 4H, Ar-H), 7.17(s, 1H, NH), 5.47(bs, 1H, 5.45(d, J=10.45Hz, 1H, CH), 2.36(s, 3H, CH_3), 2.13(s, 3H, CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3325, 3284, 3259, 2939, 1703, 1680, 1606, 1525, 1460, 1423, 1375, 1329, 1238, 769, 709; Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17% Found: C, 67.85; H, 6.18; N, 12.14%.

5-Aceto 6-methyl-2-thio-4-phenyl-1, 2, 3, 4-tetrahydropyridimidine (13).
^{1}H NMR ($CDCl_3$): δ(ppm)=7.53(bs, 1H, NH), 7.34(m, 5H, Ar-H), 7.06(s, 1H, NH), 5.47(s, 1H, CH), 2.36(s, 3H, CH_3), 2.15(s, 3H, CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3294, 3205, 3122, 2999, 1602, 1456, 1332, 1251, 1188, 769, 702; Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37% Found: C, 63.36; H, 5.77; N, 11.32%.

5-Aceto-6-methyl-2-oxo-4(4-chlorophenyl) 1, 2, 3, 4-tetrahydropyridimidine (14).

^{1}H NMR($CDCl_3$): δ(ppm)=7.84(s, 1H, NH), 7.23-7.35(m, 4H, Ar-H), 5.60(bs, 1H, NH), 5.46(s, 1H, CH), 2.35(s, 3H, CH_3), 2.17(s, 3H, CH_3); IR ($CDCl_3$): (KBr) (ν_{max} cm-1) 3288, 3217, 3119, 2945, 1701, 1618, 1465, 1327, 1236, 831, 794; Anal. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58% Found: C, 59.02; H, 4.91; N, 10.61%.

CONCLUSION

One pot multicomponent reaction promoted by the synergy of combined use of Chlorosulphonic acid and ultrasound offers an easy access to substituted DHPMs in excellent yields. The products can be easily isolated by simple workup procedures such as dilution and filtration of the precipitated product (DHPMs). A quick and an efficient multicompnent synthesis, applying ultrasound-induced Biginelli condensation allows rapid formation of small libraries of medicinally interesting podands.

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