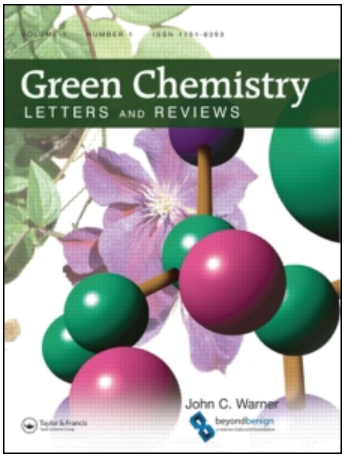

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A very high yielding and facile alkaline earth metals homogeneous catalysis of Biginelli reaction: an improved protocol

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ORIGINAL ARTICLE

A very high yielding and facile alkaline earth metals homogeneous catalysis of Biginelli reaction: an improved protocol

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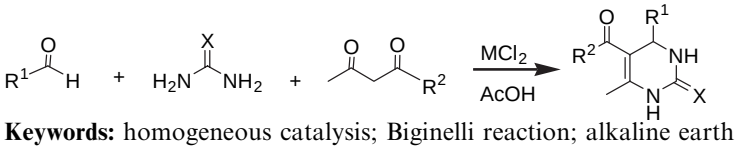
A high yielding and facile Biginelli reaction for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones, using inexpensive and available alkaline earth metal chlorides ($MgCl_2$, $CaCl_2$, $SrCl_2$ and $BaCl_2$) and acetic acid as the solvent in a homogeneous catalytic reaction, is reported.



Keywords: homogeneous catalysis; Biginelli reaction; alkaline earth metals

Introduction

In recent years, dihydropyrimidin-2(1H)-ones and thiones have occupied an important place in synthetic organic chemistry due to their pharmacological and therapeutic properties (*1*). They have served as integral backbones of several calcium channel blockers, antihypertensive agents, α-1-antagonists and neuropeptideY (NPY) antagonists (*2*). Several isolated marine alkaloids with biological activities have also been found to contain the dihydropyrimidinones-5-carboxylate core (*3*). Due to the importance of these compounds as synthons in organic synthesis, many methods for preparation of such compounds have been developed, and the Biginelli reaction has gained particular importance for ongoing research programs (*4*).

Alkaline earth metals chloride have been utilized for various organic reactions. $MgCl_2$ has been used for aldol reaction of α-dimethylsilylesters with aldehydes, ketones and α-enones(*5*). Theoretical study on dehydration process of $MgCl_2{\cdot}6H_2O$ (*6*) have also been developed. $CaCl_2$ has been reported to be useful in preservation of protective group in peptide synthesis, (*7*) and aldol type reaction of unprotected sugars in methanol (*8*). The Biginelli reaction catalyzed by calcium chlorides under microwave assisted (*9a*) and reflux condition in ethanol (*9b*) has also been disclosed. $SrCl_2$ has been introduced accompanied with HCl in the synthesis of dehydropyrimidinones (*10*).

In continuation of our interest in catalytic reactions, (*11*) in this communication we wish to reveal our studies in catalytic activity of some alkaline earth metals chloride ($MgCl_2$, $CaCl_2$, $SrCl_2$ and $BaCl_2$) in the reaction of various aromatic and aliphatic aldehydes, ethyl and methyl acetoacetate, with urea and thiourea in acetic acid for the known and useful Biginelli reaction (Scheme 1).

Results and discussions

Homogeneous catalysts have been offered a number of important advantages over their heterogeneous counterparts. For example, in homogeneous catalysis all catalytic sites for reactants are accessible. Therefore, they are higher yielding, more selective, reactive and easily studied from chemical mechanistic aspects for a single product, and more easily modified for optimizing selectivity. One of main disadvantage of homogeneous catalysis is the problem of product/catalyst separations. This drawback makes heterogeneous catalysis a better choice for chemical industries.

The original one pot three-component synthesis of 3,4-dihydropyrimidin-2(1H)-ones was first reported by Peitro Biginelli in 1893 using homogeneous Bronsted acid catalysis (*12*).

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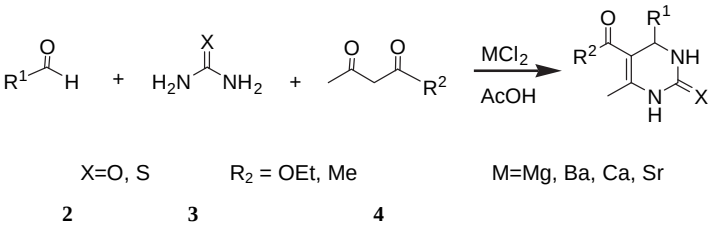


Scheme 1. The synthesis of dihydropyrimidinones and thiones using metal earth chlorides

A serious limitation of this protocol is that it produces low yields of desired heterocycles when substituted aromatic and aliphatic aldehydes were used. Since then, many heterogeneous catalysis has been revealed for this important reactions which have their own merits and drawbacks (*13–16*). Furthermore environmental and economical aspects must be the prime consideration to redesign commercially important processes.

Alkaline earth metal chlorides not only are readily available and inexpensive, but also exhibit substantial stability and solubility. The exceptional feature of using $MgCl_2$, $CaCl_2$, $SrCl_2$ and $BaCl_2$ is solubility in acetic acid, as ions M^{2+} and Cl^{1-}, which is an inexpensive and available solvent. However the products of Biginelli reactions are insoluble in this solvent. These chances and opportunities can circumvent the problem of separation of product/catalyst in homogeneous catalysis while keeping all of the reaction's other advantages.

We used the aforementioned alkaline earth metal halides in the Biginelli reactions in catalytic amounts. All of them nearly catalyzed this reaction at the same conditions (Table 1). Our approaches preserved the simplicity of heterogeneous catalyzed Biginelli reaction not only from simple separation processes but also consistently provide excellent yields (with an error $+/-2\%$).

It is noteworthy to mention that the boiling of the reactants in acetic acid at reflux temperature without catalysts resulted in poor yields of products even in prolonged reaction times.

The reactions were examined in ethanol and tetrahydrofuran under reflux conditions (Table 2). The results in Table 2, showed that when we used acetic acid as a solvent, the reactions proceeded under milder conditions and with shorter reaction times in comparison with using other solvents including ethanol and THF. Using DMSO as a higher boiling point solvent did not improve the yields and reaction times. It is also noteworthy to mention that the reactions are heterogenous in the presence of $BaCl_2$, $SrCl_2$, $MgCl_2$ in THF, EtOH, and DMSO but homogenous in acetic acid. We observed $MgCl_2$ as

Table 1. Metal earth alkaline chloride catalyzed synthesis of dihydropyrimidinones and thiones.

				Time(min)/Yield%				M. P. (°C)	
Entry	R_1	R_2	X	$MgCl_2.6H_2O$	$CaCl_2.6H_2O$	$SrCl_2.6H_2O$	$BaCl_2.6H_2O$	Observed	Reported
1	C_6H_5–	OEt	O	45/90	65/90	75/84	30/90	201–204	200–202 (*32*)
2	4-Cl–C_6H_4–	″	O	50/87		90/91	45/81	214–217	215–216 (*32*)
3	3-Nitro–C_6H_4–	″	O	45/91		60/89	30/92	225–228	226–227 (*28*)
4	4-MeO–C_6H_4–	″	O	60/86	60/83	60/89	60/86	202–204	201–202 (*39*)
5	C_6H_5–CH =CH–	″	O	90/85				230–235	238–239 (*39*)
6	$CH_3CH_2CH_2$–	″	O	90/88				152–154	153–155 (*31*)
7	CH_3CH_2–	″	O	75/93				171–174	170–172 (*31*)
8	$(CH_3)_2CH$–	″	O	90/85				170–173	170–172 (*31*)
9	C_6H_5–	″	S	90/84			120/83	209–211	208–210 (*39*)
10	4-Cl–C_6H_4–	″	S	60/82			120/78	191–195	192–195 (*39*)
11	4-MeO–C_6H_4–	″	S	75/88			90/86	155–156	153–155 (*37*)
12	4-Me–C_6H_4–	OEt	O		65/90	60/88	60/93	215–217	214–216 (*37*)
13	4-MeO–C_6H_4–	OMe	O		60/87	60/91	60/85	191–193	192–194 (*21*)
14	C_6H_4–	″	O		60/81	75/93	60/90	209–211	209–212 (*31*)
15	4-Cl–C_6H_4–	″	O			75/96	45/88	204–205	204–207 (*21*)
16	3-Br–C_6H_4–	OEt	O			90/93		185–186	185–186 (*31*)
17	4-Nitro–C_6H_4–	OMe	O				60/87	236–238	235–237 (*21*)

Table 2. Synthesis of 5-ethoxy carbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H) one using solvents of lower and higher boiling points than acetic acid in the presence of MCl_2 under reflux condition.

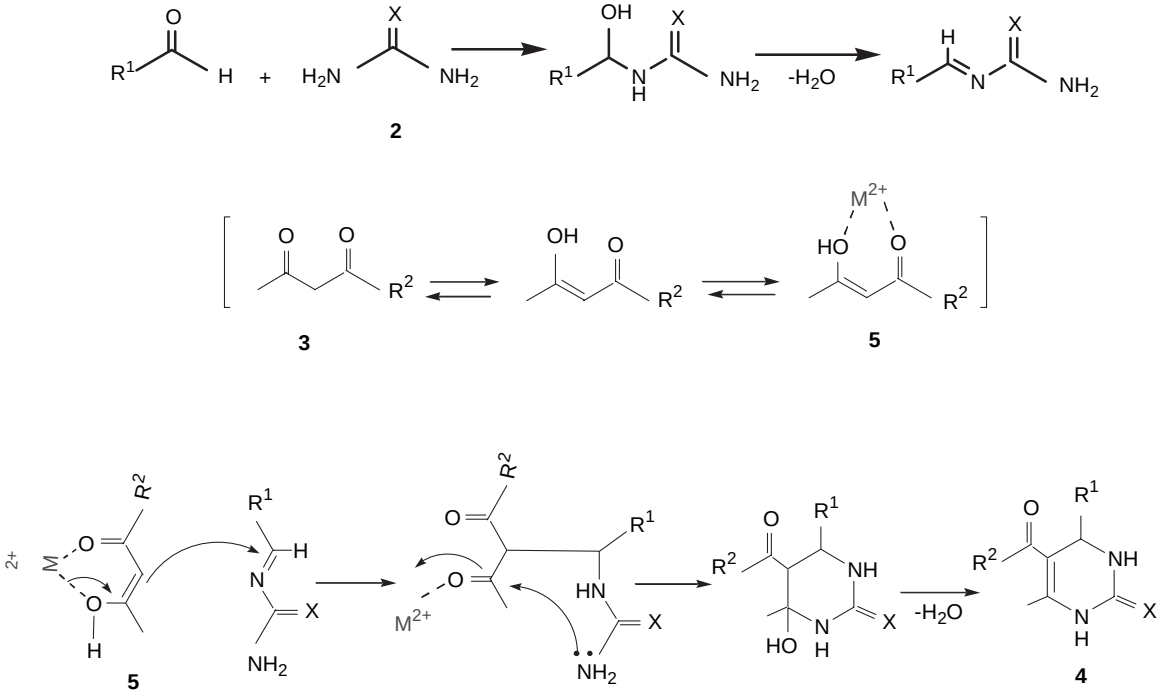
Entry	Solvent	$MgCl_2$ Time/Yield (%)	$CaCl_2$ Time/Yield (%)	$SrCl_2$ Time/Yield (%)	$BaCl_2$ Time/Yield (%)
1	AcOH	45 min/90	60min/81	75min/93	60min/90
2	THF	9h/60	8h/70	10h/82	12.5h/75
3	EtOH	8h/50	7h/84	9h/91	12h/75
4	DMSO	2h/82	2h/75	3h/80	3/85

a heterogenous catalyst in THF and ethanol was much more inferior than the other salts. However we do not have reasonable comment for such a case.

The plausible mechanism is given below. In this mechanism, (*37*) the first step of the reaction between aldehyde **1** and urea (thiourea) **2** includes the formation of Schiff's base on the α-olefinic carbon of tautomer followed by β-carbonyl carbon attack on imine-carbon to give a six-member heterocyclic compound, which on dehydration leads to our target dihydropyrimidinones **4**. By considering the alkaline earth metal chlorides as Lewis acid, a tautomer **5** can be formed and stabilized by an alkaline earth metal chloride (Scheme 2).

In order to show the merits of this homogeneous catalysis in comparison with some reported protocols, using heterogeneous catalysis, we compared the results of the formation of 5-ethoxy carbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H) one (Entry 1, Table 1) in the presence of montmorillonit-KSF, sulfuric acid, zeolite, heulandite, silica sulfuric acid, $BF_3.OEt_2$/CuCl, kaolin, and two heteropolyacids (Table 3). From the results given in Table 3, the advantages of our method are evident, regarding the yields of the reactions which are very important in chemical industry especially when it is combined with easy separation. Also, our protocol has developed the synthesis of 5-ethoxy carbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H) one in term of reaction times (Table 3).

It is worthwhile to mention the superior role of acetic acid in these reactions as a solvent. It provides a homogenous media for the reaction as it dissolves both reagents and catalyst and makes the homogenous conditions ready. In addition, after completion of the reaction it can be neutralized, to dissolve the inorganic salts and leave the organic materials more separable by organic solvents. Another merit of this



Scheme 2. The suggested mechanism for earth alkaline metals chloride homogeneous catalyzed Biginelli reaction.

Table 3. The various catalysts, were used in one-pot three component synthesis of 5-ethoxy carbonyl-4-phenyl-6-methyl-3, 4-dihydropyrimidin-2(1H) one.

Entry	Catalyst	Reference	Yield (%)	Condition Time(h)/δ°C/Solvent
1	Montmorillonite-KSF	18	38	48 /100/H_2O
2	Zeolite	17	21	12/reflux/toluene
3	Heulandite	4a	75	4–5/100/AcOH
4	12-tungestanphosphoric acid	4b	75	6–7/reflux/AcOH
5	12-Molybdophosphoric acid	20	80	5/reflux/AcOH
6	Silica Sulfuric acid	19	91	6/reflux/EtOH
7	$BF_3.OEt_2$/CuCl	21	71	18/reflux/THF
8	FAP[a]	22	18	70/reflux/toluene
9	$ZnCl_2$/FAP	″	90	″
10	$CuCl_2$/FAP	″	76	″
11	$NiCl_2$/FAP	″	73	″
12	p-Toluenesulfonic acid	23	90	0.25/r.t/water
13	I_2	24	95	4/reflux/toluene
14	$InBr_3$	25	98	7/reflux/THF
15	$ZnCl_4$	26	90	4/reflux/EtOH
16	$RuCl_3$	27	91	0.5/100°C/–
17	NBS	28	94	10/reflux/EtOH
18	$LaCl_3$	29	95	5/reflux/EtOH
19	$LiClO_4$	30	89	5/reflux/MeCN
20	$NiCl_2$	31	94	4/reflux/EtOH
21	$CuCl_2/CuSO_4$	32	98	1/100°C/–
22	$Bi(OTf)_3$	33	90	1/r.t/MeCN
23	$BiCl_3$	34	95	5/reflux/MeCN
24	$FeCl_3{\cdot}6H_2O$	35	93.8	4/reflux/EtOH
25	$KHSO_4$	36	95	0.5–2/100°C/Glycol
26	$CdCl_2$	37	83	4/reflux/MeCN
27	$InCl_3$	38	75	7/reflux/THF

[a]Fluorapatite.

neutralization and separation from the environmental point of view is to convert acetic acid to less hazardous acetates.

Conclusion

In summary we have developed a high yielding and relatively eco-friendly homogeneous catalysis of the Biginelli reaction for the synthesis of dihydropyrimidinones in excellent yields. The easy separation of product/catalyst is the key factor of this methodology.

Experimental section

Melting points were read using Barenstead Electrothermal apparatus. IR spectra were recorded on Bruker Tensor 27. IR spectrometer did scanning between 4000–400 cm^{-1}. ^1H NMR spectra were obtained on Bruker AQS AVANCE-300MHZ NMR instrument.

All starting materials purchased from Aldrich Company and are used without more purification. Also acetic acid was in reagent grade.

Preparation of 3,4-dihydropyrimidin-2(1H)-ones and thiones: A typical procedure

In a three-neck round bottomed flask, equipped with condenser and thermometer, an appropriate aldehyde (1 mmol), ethyl acetoacetate or methyl acetoacetate (1 mmol), urea or thiourea (1.2 mmol), $MgCl_2$ (0.1 mmol), in acetic acid (5 mL) were stirred at reflux temperature for 45–120 minutes (Table 1). Upon completion of the reaction, monitored by TLC (eluent: n-hexane: ethyl acetate, 4:1), the reaction mixture was neutralized with 10% sodium bicarbonate (15 mL). The residue was poured onto crushed ice and was filtered to give the crude product, which was further purified by recrystallization from MeOH.

Physical and spectral data

5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 1)**. Solid: mp 201–204°C (lit. (*22*) 200–202); IR (KBr disc) ν_{max}/cm^{-1}: 3414, 3230, 3109, 2936, 1702, 1649,1599; ^1H NMR (300 MHz, DMSO-*d*6) δ(Hz) 9.17(s, 1H), 7.72(s, 1H),

7.21–7.32(m, 5H), 5.14(s, 1H), 3.98(q, 2H), 2.24 (S, 3H), 1.08(t, 3H).

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one **(entry 2)**. Solid; mp 214–217°C (Lit. (*18*) mp 215–216°C); IR(KBr disc) ν_{max}/cm^{-1}: 3419, 3246, 3112, 2980, 1708, 1646, 1487; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.23 (s, 1H), 7.75 (s, 1H), 7.38 (d, 2H), 7.24 (d, 2H), 5.14 (d, 1H), 3.97 (q, 2H), 2.24 (s, 3H), 1.08 (t, 3H).

5-Ethoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one **(entry 3)**. Solid; mp 225–228°C (Lit. (*28*) mp 226–227°C); IR (KBr disc) ν_{max}/cm^{-1}:3270, 1691, 1676, 1615, 1513; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.37 (s, 1H), 7.9 (s, 1H), 8.09–7.64 (m, 4H), 5.29 (s, 1H), 3.98 (q, 2H), 2.26 (s, 3H), 1.07 (t, 3H).

5-Ethoxycarbonyl-4-(4-methoxylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 4)**. Solid; mp 202–204°C (lit. (*27*)201–202); IR(KBr disc) ν_{max}/cm^{-1}: 3415, 3241, 3114, 2954, 1708, 1646, 1512; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.14(s, 1H), 7.66(s,1H), 7.14(d, 2H), 6.86(d, 2H), 5.08(d, 1H), 3.97(q, 2H), 3.71(s, 3H), 2.23 (s, 3H), 1.09 (t, 3H).

5-Ethoxycarbonyl-4-(cinnamyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 5)**. Solid; mp 230–235°C (Lit. (*39*) mp 238–239°C); IR(KBr disc) ν_{max}/cm^{-1}: 3383, 3215, 3105, 3012, 1700, 1646; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 8.55 (s, 1H), 6.30 (s, 1H), 7.30–7.014 (m, 5H), 6.38(dd, 1H), 6.02(dd, 1H), 4.31 (s, 1H), 4.15(q, 2H), 2.28 (s, 3H), (t, 3H).

5-Ethoxycarbonyl-4-(n-propyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 6)**. Solid; mp 152–154°C (Lit. (*17*) mp 153–155°C); IR(KBr disc) ν_{max}/cm^{-1}: 3414, 3247, 3119, 1709, 1676, 1646; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 8.55 (s, 1H), 6.30 (s, 1H), 4.31 (s, 1H), 4.15(q, 2H), 2.28 (s, 3H), 1.40–1.59 (m, 4H), 1.28 (t, 3H), 0.90 (t, 3H).

5-Ethoxycarbonyl-4-(ethyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 7)**. Solid; mp 209–211°C (Lit. (*31*) *mp 208–210°C); IR(KBr disc)* ν_{max}/cm^{-1}*: 3248, 3120, 2464, 1717, 1646, 1471;* ^{1}*H NMR (300 MHz, DMSO-d*6) δ (Hz) 8.24 (s, 1 H), 6.04 (s, 1 H), 4.19 (m, 1H), 4.08 (q, 2H), 2.20 (s, 3H), 1.52 (m, 2H), 1.19 (t, 3H), 0.83 (t, 3H).

5-Ethoxycarbonyl-4-(iso propyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 8)**. Solid; mp 170–173°C (Lit. (*17*) mp 170–172°C); IR(KBr disc) ν_{max}/cm^{-1}: 3413, 3237, 3106, 1700, 1646; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 8.61 (s, 1 H), 6.31 (s, 1H), 4.23 (s, 1H), 4.16(q, 2H), 2.29 (s, 3H), 1.85 (m, 1H), 1.28 (t, 3H), 0.91 (d, 3H), 0.86 (d, 3H).

5-Ethoxycarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione **(entry 9)**. Solid; mp 209–211°C (Lit. (*35*) mp 208–210°C); IR(KBr disc) ν_{max}/cm^{-1}: 3416, 3229, 3104, 2939, 1701, 1650,1589; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 8.89 (s, 1H), 7.72(s,1H), 7.21–7.32(m, 5H), 5.14(s, 1H), 3.98 (q, 2H), 2.24(S, 3H), 1.08(t, 3H).

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-thione **(entry 10)**. Solid; mp 191–195°C (Lit. (*35*) mp 192–195°C); IR(KBr disc) ν_{max}/cm^{-1}: 3415, 3256, 3111, 2988, 1701, 1649, 1487; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.1 (s, 1H), 8.68(s, 1H), 7.38 (d, 2H), 7.24 (d, 2H), 5.14 (d, 1H),3.97 (q, 2H), 2.24 (s, 3H), 1.08 (t, 3H).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione **(entry 11)**. Solid; mp 155–156°C (Lit. (*37*) mp 153–155°C); IR(KBr disc) ν_{max}/cm^{-1}: 3157, 3122, 1710, 1651, 1596; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 10.37 (s, 1H), 9.71(s, 1H), 7.27 (dd, 2H), 6.84 (dd, 2H), 5.90 (s, 1H), 4.03 (q, 2H), 3.73 (s, 3H), 2.30 (s, 3), 1.12 (t, 3H)

5-Ethoxycarbonyl-4-(*p*-tolyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 12)**. Solid; mp 215–217°C (Lit. (*33*) mp 214–216°C); IR(KBr disc) ν_{max}/cm^{-1}: 3415, 3241, 3114, 2954, 1708, 1646,1512; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.14(s, 1H), 7.66(s,1H), 7.14(d, 2H), 6.86(d, 2H), 5.08(d, 1H), 3.97(q, 2H), 3.71(s, 3H), 2.23 (s, 3H), 1.09 (t, 3H).

5-Methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 13)**. Solid; mp 192–194°C (Lit. (*17*) mp 192–194°C); IR(KBr disc) ν_{max}/cm^{-1}: 3415, 3247, 3111, 2953, 1719, 1683, 1512; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.20 (s, 1H), 7.70 (s, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.08 (d, $J = 2.8$ Hz, 1H), 3.72 (s, 3H), 3.52 (s, 3H), 2.24 (s, 3H).

5-Methoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 14)**. Solid; mp 209–211°C (Lit. (*17*) mp 209–211°C); IR(KBr disc) ν_{max}/cm^{-1}: 3332, 3223, 3105, 2948, 1697, 1666; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.24 (s, 1H), 7.70 (s, 1H), 7.34–7.22 (m,5H), 5.14 (d, $J = 2.8$ Hz, 1H), 3.53 (s, 3H), 2.25 (s, 3H).

5-Methoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 15)**. Solid; mp 204–205°C (Lit. (*17*) mp 205–207°C); IR(KBr disc) ν_{max}/cm^{-1}: 3364, 3221, 3103, 2947, 1712, 1636, 1494; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.30 (s, 1H), 7.82 (s, 1H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 2H), 5.14 (d, $J = 2.8$ Hz, 1H), 3.53 (s, 3H), 2.25 (s, 3H).

5-Methoxycarbonyl-4-(3-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(entry 16)**. Solid; mp 185–186°C (Lit. (*31*) mp 185–186°C); IR(KBr disc) ν_{max}/cm^{-1}: 3416, 3228, 3113, 2976, 2932, 1705, 1654, 1613,1589; ^{1}H NMR (300 MHz, CDCl3) δ (Hz) 9.26 (s, 1H), 7.78 (s, 1H), 7.22–7.45 (m, 4H), 5.14 (d, $J =$

3.2 Hz, 1H), 3.95 (q, $J = 7.2$ Hz, 2H), 2.25 (s, 3H), 1.09 (t, $J = 7.2$ Hz, 3H).

5-Methoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one **(entry 17)**. Solid; mp 236–238°C (Lit. (*17*) mp 235–237°C); IR(KBr disc) ν_{max}/cm^{-1}: 3364, 3222, 3113, 2949, 1717, 1640, 1516; ^{1}H NMR (300 MHz, DMSO-*d*6) δ (Hz) 9.41 (s, 1H), 8.22 (d, $J = 8.4$ Hz, 2H), 7.93 (s, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 5.27 (d, $J = 2.8$ Hz, 1H), 3.54 (s, 3H), 2.27 (s, 3H).

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References

(1) (a) Studer, A.; Jeger, P.; Curran, D.P.; *J. Org. Chem.* **1997**, *62*, 2917; (b) Kappe, C.O.; *Acc. Chem. Res.* **2000**, *33*, 879–888.

(2) (a) Atwal, K.S.; Swanson, B.N.; Unger, S.E.; Floyed, D.M.; Moreland, S.; Hedberg, A.; O,Reilly, B.C.; *J. Med. Chem.* **1991**, *34*, 806–811; (b) Rounyak, G.C.; Atwal, K.S.; Hedberg, A.; Kimball, S.D.; Moreland, S.; Gougoutas, J.Z.; O'Reilly, B.C.; Schwart, J.; Malley, M.; *J. Med. Chem.* **1992**, *35*, 3254–3263; (c) Rounyak, G.C.; Kimball, S.D.; Beyer, B.; Cucinotta, G.; Dimarco, J.D.; Gougoutas, J.Z.; Hedberg, A.; Malley, M.; Mccathy, J.P.; Zhang, R.; Moreland, S.; *J. Med. Chem.* **1995**, *38*, 119–129; (d) Kappe, C.O.; Fabian, W.M.F.; Semones, M.A.; *Tetrahedron* **1997**, *53*, 2803–2816.

(3) (a) Sinder, B.; Shi, Z.; *J. Org. Chem.* **1993**, *58*, 3828–3839; (b) Overman, L.E.; Rabinowitz, M.H; Renhowe, P.A.; *J. Am. Chem. Soc.* **1995**, *117*, 2657–2658.

(4) (a) Tajbakhsh, M.; Mohajerani, B.; Heravi, M.M.; Ahmadi, A.N.; *J. Mol. Catal. A-Chem.* **2005**, *236*, 216–219; (b) Heravi, M.M.; Derikvand, F.; Oskooie, H.A.; Hekmat Shoar, R.; Bamoharram, F.F.; *J. Mol. Catal. A- Chem.* **2005**, *242*, 173–175; (c) Singh, V.; Sapehiyia, V.; Srivastava, V.; Kaur, S.; *Catal Commun.* **2006**, *7*, 571–578; (d) Zhang, X.; Li, Y.; Liu, C.; Wang, J.; *J. Mol. Catal. A-Chem.* **2006**, *253*, 207–211; (e) Bose, D.S.; Chary, M.V.; Mereyala, H.B.; *Heterocycles* **2006**, *68*, 1217; (f) Jain, S.L.; Sharma, V.B.; Sain, B.; *J. Heterocycl. Chem.* **2006**, *43*, 777–779; (g) Savegnago, Nogueira, C.W.; *Eur. J. Med. Chem.* **2006**, *41*, 513–518; (h) Rafiee, E.; Shahbazi, F.; *J. Mol. Catal. A-Chem.* **2006**, *250*, 57–61; (i) Kapoor, K.K.; Ganai, B.A.; Kumar, S.; Andotra, C.S.; *Can. J. Chem.* **2006**, *84*, 433–437; (j) Roy, D.K.; Bordoloi, *Indian J. Chem. B.* **2006**, *45*, 1067–1071; (k) Pasha, M.A.; Puttaramegowda, J.V.; *Heterocycl. Commun.* **2006**, *12*, 61–66; (l) Saini, A.; Kumar, S.; Sandhu, J.S.; *Indian J. Chem. B.* **2006**, *45*, 684–688; (m) Su, W.-K.; Li, J.-J.; Zheng, Z.-G.; Shen, Y.-C; *Tetrahedron Lett.* **2005**, *46*, 6037–6040; (n) Chen, X.-H. Xu, X.-Y.; Liu, H.; Cun L.-F.; Gong, L.-Z.; *J. Am. Chem. Soc.* **2006**, *128*, 14802–14803; (o) Russowsky, D.; Lopes, F.A.; da Silva, V.S.S.; Canto, K.F.S.; Montes D'Oca, M.G.; Godoi, M.N.; *J. Braz. Chem. Soc.* **2004**, *15*, 165–169;(p) Xia, M.; Wang, Y.G.; *Tetrahedron Lett.* **2002**, *43*, 7703–7705; (q) Xu, H.; Wang, Y.G.; *Chin. J. Chem.* **2003**, *21*, 327–331.

(5) Mitra, K.; Nakagawa, T.; Hosomi, A.; *Synlett.* **2005**, 1917–1927.

(6) Liu, G.S.; Song, X.F.; YU, J.G.; *Mater Sci forum.* **2005**, *488*, 53–55.

(7) Pascal, R.; Sala, R.; *Tetrahedron Lett.* **1998**, *39*, 5031.

(8) Saimato, H.; Tatoni, S.; Sashira, H.; Shygimasa, V.; *Tetrahedron Lett.* **1995**, *36*, 937–938.

(9) (a) Misra, A.K.; Agnihotri, G.; Mashusudan, S.K.; *Ind. J. Chem.* **2004**, *45B*, 2018–2020; (b) Gangadasu, B.; Narender, P.; Raju, B.C.; Rao, V.J.; *Ind. J. Chem. B.* **2006**, *45*, 1259–1263; (c) Shaabani, A.; Bazgir, A.; Arab-Ameri, S.; Kiasaraie, M.S.; Samadi, S.; *Iranian J Chem Chemical Eng-International English Edition* **2005**, *24*, 67–71.

(10) Esfahani, M.N.; Khosropour, A.R.; *Bull Korean Chem. Soc.* **2005**, *26*, 1331–1332.

(11) (a) Heravi, M.M.; Behbahani, F.K.; Zadsirjan, V.; Oskooie, H.A.; *Heterocyclic Commun.* **2006**, *12*, 369–372; (b) Heravi, M.M.; Bakhtiari, K.; Bamoharram, F.F.; *Catalysis Commun.* **2006**, *7*, 373–376; (c) Heravi, M.M.; Derikvand, F.; Bamoharram, F.F.; *J Mol Catal Chem* **2005**, *242*, 173–175; (d) Tajbakhsh, M.; Mohajerani, B.; Heravi, M.M.; Ahmadi, A.N.; *J Mol Catal Chem* **2005**, *236*, 216–219.

(12) Biginelli, P.; *Gazz. Chim. Ital.* **1893**, *23*, 360–416.

(13) Rani, V.R.; Srinivas, N.; Kishan, M.R.; Kulkarni, S.J.; Raghavan, K.V.; *Green Chem.* **2001**, *3*, 305–306.

(14) Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G.; *Tetrahedron Lett.* **1999**, *40*, 3465–3468.

(15) Salehi, P.; Dabiri, M.; Zolfigol, M.A.; Bodaghi Fard, A.; *Tetrahedron Lett.* **2003**, *44*, 2889–2891.

(16) Heravi, M.M.; Bakhtiari, K.; Bamoharram, F.F.; *Catalysis Commun.* **2006**, *7*, 373–376.

(17) Hu, E.H.; Sidler, D.R.; Dolling, U.H.; *J. Org. Chem.* **1998**, *63*, 3454–3557.

(18) El Badaoui, H.; Bazi, F.; Tahir, R.; Lazrek, H.B.; Sebti, S.; *Catalysis Commun.* **2005**, *6*, 455–458.

(19) Bose, A.K.; Manhas, M.S.; Pednekar, S.; Ganguly, S.N.; Dang, H.; He, W.; Mandadi, A.; *Tetrahedron Lett.* **2005**, *46*, 1901–1903.

(20) Srinivas, K.V.N.S.; Das, B.; *Synthesis.* **2004**, 2091–2093.

(21) Nan-Yan Fu, Yao-Feng Yuan, Cao, Z.; Wang, S.; Wang, J.; Peppe, C.; *Tetrahedron.* **2002**, *58*, 4801–4807.

(22) Venkatesshwar, Reddy, C.; Mahesh, M.; Raju, P.V.K.; Ramesh, Babu, T.; Narayana, Reddy, V.V.; *Tetrahedron Lett.* **2002**, *43*, 2657.

(23) Surya, K.; Richard, D.; Gibbs, A.; *Synthesis.* **2005**, *11*, 1748–1750.

(24) Hazarkhani, H.; Karimi, B.; *Synthesis.* **2004**, *8*, 1239–1242.

(25) Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H.; *Tetrahedron Lett*. **2000**, *41*, 9075–9078.
(26) Yadav, S.; Jhillu, S.; Reddy, V.; Basi, R.; Venugopal, C.; Ramalingam, T.; *Synthesis*. **2001**, *9*, 1341–1345.
(27) Lu, J.; Bai, Y.; *Synthesis*. **2002**, 466–470.
(28) Gohain, M.; Prajapati, D.; Sandhu, Jagir, S.; *Synlett*. **2004**, 235–238.
(29) Varala, R.; Alam, M.M.; Adapa, S.R.; *Synlett*. **2003**, 67–70.
(30) Ramalinga, K.; Vijayalakshmi, P.; *Synlett*. **2001**, 863–865.
(31) Lu, J.; Ma, H.; *Synlett*. **2000**, *1*, 63–64.
(32) Tu, S.; Fang, F.; Zhu, S.; Li, T.; Zhang, X.; Zhuang, Q.; *Synlett*. **2004**, *3*, 537–39.
(33) Venkat, A.; Narsaiah, A.K.; Basak, K.; *Nagaiah, Synthesis*. **2004**, *8*, 1253–1256.
(34) Runu, B.C.; Hajra, A.; Jana, U.; *J. Org. Chem*. **2000**, *65*, 6270–6272.
(35) Paraskar, A.S.; Dewkar, G.K.; Sudalai, A.; *Tetrahedron Lett*. **2003**, *44*, 3305–3308.
(36) Kappe, C.O.; Kumar, D.; Varma, R.S.; *Synthesis*. **1999**, 1799–1803.
(37) Gangadasu, B.; Palaniappan, S.; Jayathirtha Rao, V.; *Synlett*. **2004**, *7*, 1285–1287.
(38) Kumar Mitra, A.; Banerjee, K.; *Synlett*. **2003**, 1509–1511.
(39) Folkers, K.; Harwood, H.J.; Johnson, T.B.; *J. Am. Chem. Soc*. **1932**, *54*, 3751–3758.