

# Chlorosulfonic acid catalyzed highly efficient solvent-free synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones

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**Summary.** Chlorosulfonic acid (ClSO<sub>3</sub>H) is used as an alternative to conventional acid catalyst in the Biginelli reaction of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea. This method gives the desired dihydropyrimidines in higher yields under solvent-free conditions in shorter time.

**Keywords:** ClSO<sub>3</sub>H catalyst, Biginelli reaction.

In 1893 Biginelli [1] reported the first synthesis of dihydropyrimidinone by refluxing a mixture of an aldehyde, a  $\beta$ -ketoester and urea under strongly acidic condition. Dihydropyrimidinones and their sulphur analogues are pharmacologically important because of their antibacterial, antitumour and anti-inflammatory properties [2]. Many of these compounds act as antihypertensive agents as well as calcium channel blocker-1a-antagonists and neuropeptide Y (NPY) antagonists [3]. The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety in the molecule [4]. Hence synthesis of these dihydropyrimidines and thiones has gained much importance in recent years. However, it suffers from low yields of the product particularly in the case of substituted aromatic and aliphatic aldehydes. Recently several methods have been reported for preparing dihydropyrimidines using different Lewis acids such as BF<sub>3</sub>·xOEt<sub>2</sub> [5a], LaCl<sub>3</sub> [5b], Yb(OTf)<sub>3</sub> [5c], La(OTf)<sub>3</sub> [5d], InBr<sub>3</sub> [5e], BiCl<sub>3</sub> [5f], Bi(OTf)<sub>3</sub> [5g],

LiBr [5h], LiClO<sub>4</sub> [5i], Mn(OAc)<sub>3</sub>·x2H<sub>2</sub>O [5j], cerium ammonium nitrate [5k], FeCl<sub>3</sub>·x6H<sub>2</sub>O, NiCl<sub>2</sub>·x6H<sub>2</sub>O [5l], silica sulfuric acid [5m], VCl<sub>3</sub> [5n] etc. as well as protic acids such as H<sub>2</sub>SO<sub>4</sub>, HOAc, Conc. HCl [6] as promoters. Many other methods including microwave irradiations, ionic liquids and clay [7] are also reported. However, many of these methods are associated with expensive and toxic reagents, stoichiometric amount of catalyst, reaction time, unsatisfactory yields, incompatibility with other functional groups and involve difficult product isolation procedures. Moreover, some of the methods are practical for aromatic aldehydes only [5 a, k; 8]. Thus, there is still a need for a simple and general procedure for one-pot synthesis of dihydropyrimidinone and thiones under mild conditions.

Chlorosulfonic acid was discovered in 1854 and soon became a reagent of widespread use. It has found application in many diverse types of reaction, such as alkylation, halogenation, rearrangement, cyclization and polymerization, usually operating as a strong acid catalyst and efficient halogenating and dehydrating agent [9].

Here we report a simple and efficient method for the synthesis of 3,4-dihydropyrimidines using chlorosulfonic acid as a catalyst. The three component mixture of aldehyde, 1,3-dicarbonyl

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Physical data of dihydropyrimidinones and thiones

Entry	R <sup>1</sup>	R <sup>2</sup>	X	Time (min.)		Yield (%)		M.P. (°C)
				Experimental	Reported	Found	Reported	Found
4a	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> O	O	30	240	93	90 [10]	202-203
4b	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub> O	O	30	450	94	91 [11]	206-207
4c	4-ClC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub> O	O	35	480	95	91 [11]	213-214
4d	4-OHC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub> O	O	30	300	93	98 [10]	230-231
4e	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	C <sub>2</sub> H <sub>5</sub> O	O	45	420	86	79 [11]	152-155
4f	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub> O	O	40	60	91	91 [12]	222-225
4g	4-pyridine	C <sub>2</sub> H <sub>5</sub> O	O	50	130	88	90 [13]	186-188
4h	2-ClC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub> O	O	50	70	89	88 [12]	219-222
4i	2-furyl	C <sub>2</sub> H <sub>5</sub> O	O	40	450	92	72 [11]	204-205
4j	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub> O	O	50	100	93	93 [13]	173-176
4k	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> O	O	30	450	91	93 [11]	212-214
4l	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> O	O	40	420	91	90 [11]	238
4m	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> O	O	30	60	90	92 [12]	239-240(d)
4n	2-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> O	O	30	80	89	89 [12]	225-227
4o	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	O	40	70	89	89 [13]	231
4p	4-OHC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	O	30	140	88	94 [13]	230
4q	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	O	40	90	92	95 [12]	267-268(d)
4r	2-furyl	CH <sub>3</sub>	O	50	90	90	94 [13]	216-217
4s	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> O	S	60	300	91	90 [10]	211-213

Elemental analysis data were obtained for all the compounds and were within the limit of 0.4 % of the calculated value.

compound and urea or thiourea were heated in presence of catalytic amount of chlorosulfonic acid to give corresponding dihydropyrimidines in 85-95 % yield. In order to study the effect of substituents on the reactivity of the reactant, a variety of aliphatic and aromatic aldehydes were used. The results are given in Table 1.

In conclusion we have developed a solvent free simple and general method for chlorosulfonic acid catalyzed procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones. Its advantages are as follows: the catalyst is

inexpensive and easily available, reaction time is shorter and excellent yields are obtained.

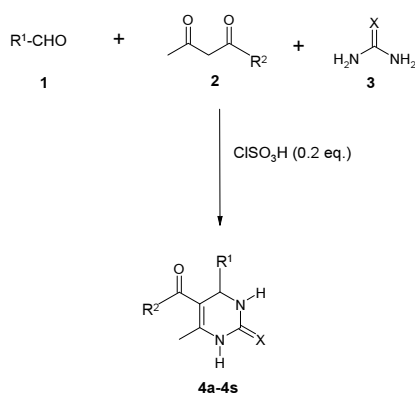
**Typical experimental procedure.** A mixture of 1,3-dicarbonylcompound (10 mM), aldehyde (10 mM), urea (15 mM) and 0.2 mM of chlorosulfonic acid was added slowly and heated at 60 °C for appropriate time as mentioned in Table 1. After completion of reaction, the reaction mixture was poured into ice water 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. <sup>1</sup>H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Electron spray ionization mass spectra (ES-MS) were recorded on Water-Micromass Quattro-II spectrometer.

**Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylate (4a).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.18 (s, 1H, NH), 7.74 (s, 1H, NH), 7.22 (m, 5H<sub>arom</sub>), 5.14 (d, 1H, J=3.6 Hz, H-4), 3.40 (q, 2H, J=6.9 Hz, OCH<sub>2</sub>), 2.24 (s, 3H, CH<sub>3</sub>), 1.09 (t, 3H, J=6.9 Hz, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 259 (M-H).

**Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-**

Scheme 1  
Facile one pot synthesis of  
3,4-dihydropyrimidin-2(1H)-ones and thiones



**tetrahydropyridimidine-5-carboxylate (4b).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.36 (s, 1H, NH), 8.23 (dd, 2H<sub>arom</sub>, J=6.9, 2.1 Hz) 7.90 (s, 1H, NH) 7.52 (dd, 2H<sub>arom</sub>, J=6.9, 2.1 Hz), 5.27 (d, 1H, J=3.0 Hz, H-4), 4.02 (q, 2H, J=7.2 Hz, OCH<sub>2</sub>), 2.26 (s, 3H, CH<sub>3</sub>), 1.12 (t, 3H, J=6.9 Hz, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 304 (M-H).

**Ethyl 6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4c).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.25 (s, 1H, NH), 7.77 (s, 1H, NH) 7.40 (d, 2H<sub>arom</sub>, J=8.7 Hz), 7.26 (d, 2H<sub>arom</sub>, J=8.4 Hz), 5.14 (d, 1H, J=3.6 Hz, H-4), 4.00 (q, 2H, J=7.2 Hz, OCH<sub>2</sub>), 2.25 (s, 3H, CH<sub>3</sub>), 1.09 (t, 3H, J=6.9 Hz, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 293 (M-H).

**Ethyl 6-methyl-4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4d).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.32 (s, 1H, OH), 9.11 (s, 1H, NH), 7.61 (s, 1H, NH), 7.04 (d, 2H<sub>arom</sub>, J=8.4 Hz), 6.70 (d, 2H<sub>arom</sub>, J=8.4 Hz), 5.04 (d, 1H, J=3.0 Hz, H-4), 3.98 (q, 2H, J=7.2 Hz, OCH<sub>2</sub>), 2.25 (s, 3H, CH<sub>3</sub>), 1.09 (t, 3H, J=8.4 Hz, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 275 (M-H).

**Ethyl 4-butyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4e).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=8.92 (s, 1H, NH), 7.31 (s, 1H, NH), 4.11 (s, 1H, H-4), 4.07 (q, 2H, J=6.9 Hz, OCH<sub>2</sub>), 2.15 (s, 3H, CH<sub>3</sub>), 1.37 (m, 2H, CH<sub>2</sub>), 1.22 (m, 4H, CH<sub>2</sub>), 1.76 (dt, 3H, J=1.5, 7.2 Hz, CH<sub>3</sub>), 0.84 (m, 3H, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 239 (M-H).

**Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4f).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.38 (s, 1H, NH), 8.15 (m, 2H<sub>arom</sub>), 7.91 (s, 1H, NH), 7.71 (m, 2H<sub>arom</sub>), 5.30 (d, 1H, J=3.3 Hz, H-4), 4.00 (q, 2H, OCH<sub>2</sub>) 2.27 (s, 3H, CH<sub>3</sub>), 1.09 (t, 3H, J=7.2 Hz, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 304 (M-H).

**Ethyl 6-methyl-4-pyridil-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4g).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.38 (s, 1H, NH), 8.50 (d, 2H<sub>arom</sub>), 7.85 (s, 1H, NH), 7.20 (d, 2H<sub>arom</sub>), 5.15 (d, 1H, J=3.3 Hz, H-4), 4.00 (q, 2H, OCH<sub>2</sub>) 2.27 (s, 3H, CH<sub>3</sub>), 1.09 (t, 3H, J=7.2 Hz, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 260 (M-H).

**Ethyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4h).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.28 (s, 1H, NH), 7.71 (s, 1H, NH), 7.28 (m, 4H<sub>arom</sub>), 5.63 (d, 1H, J=3.0 Hz, H-4), 3.90 (q, 2H, J=7.2 Hz, OCH<sub>2</sub>), 2.29 (s, 3H, CH<sub>3</sub>), 1.01 (t, 3H, J=7.2 Hz, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 293 (M-H).

**Ethyl 6-methyl-4-(2-furyl)-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4i).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.25 (s, 1H, NH), 7.70 (s, 1H, NH), 7.56 (dd, 1H<sub>arom</sub>, J=1.8, 0.9 Hz), 6.35 (dd, 1H<sub>arom</sub>, J=1.8, 3.0 Hz), 6.09 (d, 1H<sub>arom</sub>, J=3.3 Hz), 5.20 (d, 1H, J=3.3 Hz, H-4), 4.03 (q, 2H, J=7.2 Hz, OCH<sub>2</sub>), 2.22 (s, 3H, CH<sub>3</sub>), 1.16 (t, 3H, J=7.2 Hz, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 249 (M-H).

**Ethyl 6-methyl-4-(4-trifluoromethyl)-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4j).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.35 (s, 1H), 7.85 (s, 1H), 7.70 (dd, 2H), 7.45 (dd, 2H), 5.25 (d, 1H), 3.97 (q, 2H), 2.25 (s, 3H), 1.10 (t, 3H).

Mass (ES/MS): *m/z* 327 (M-H).

**Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4k).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.19 (s, 1H, NH), 7.73 (s, 1H, NH), 7.22 (m, 5H<sub>arom</sub>), 5.14 (d, 1H, J=3.6 Hz, H-4), 3.59 (s, 3H, OCH<sub>3</sub>), 2.24 (s, 3H, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 245 (M-H).

**Methyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4l).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.36 (s, 1H, NH), 8.23 (dd, 2H<sub>arom</sub>, J=6.9, 2.1 Hz) 7.90 (s, 1H, NH) 7.52 (dd, 2H<sub>arom</sub>, J=6.9, 2.1 Hz), 5.27 (d, 1H, J=3.0 Hz, H-4), 3.59 (s, 3H, OCH<sub>3</sub>), 2.26 (s, 3H, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 290 (M-H).

**Methyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4m).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.38 (s, 1H, NH), 8.15 (m, 2H<sub>arom</sub>), 7.91 (s, 1H, NH), 7.71 (m, 2H<sub>arom</sub>), 5.30 (d, 1H, J=3.3 Hz, H-4), 3.35 (s, 3H, OCH<sub>3</sub>), 2.26 (s, 3H, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 290 (M-H).

**Methyl 6-methyl-4-(2-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4n).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.28 (s, 1H, NH), 7.59 (s, 1H, NH), 7.28 (m, 4H<sub>arom</sub>), 5.63 (d, 1H, J=3.0 Hz, H-4), 3.45 (s, 3H, OCH<sub>3</sub>), 2.30 (s, 3H, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 279 (M-H).

**5-Aceto-6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine (4o).** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=9.25 (s, 1H, NH), 7.87 (s, 1H, NH) 7.40 (d, 2H<sub>arom</sub>, J=6.3 Hz), 7.26 (d, 2H<sub>arom</sub>, J=6.3 Hz), 5.24 (d, 1H, J=3.3 Hz, H-4), 2.28 (s, 3H, CH<sub>3</sub>) 2.12 (s, 3H, CH<sub>3</sub>).

Mass (ES/MS): *m/z* 263 (M-H).

**5-Aceto-6-methyl-4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine (4p).** <sup>1</sup>H NMR

(DMSO- $d_6$ ):  $\delta$ =9.36 (s, 1H, OH), 9.11 (s, 1H, NH), 7.70 (s, 1H, NH), 7.05 (d, 2H<sub>arom</sub>, J=8.4 Hz), 6.71 (d, 2H<sub>arom</sub>, J=8.4 Hz), 5.14 (d, 1H, J=3.3 Hz, H-4), 2.28 (s, 3H, CH<sub>3</sub>), 2.05 (s, 3H, CH<sub>3</sub>).

Mass (ES/MS):  $m/z$  245 (M-H).

**5-Aceto-6-methyl 4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridimidine (4q).** <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$ =9.38 (s, 1H, NH), 8.15 (m, 2H<sub>arom</sub>), 7.91 (s, 1H, NH), 7.71 (m, 2H<sub>arom</sub>), 5.30 (d, 1H, J=3.3 Hz, H-4), 2.27 (s, 3H, CH<sub>3</sub>), 2.05 (s, 3H, CH<sub>3</sub>).

Mass (ES/MS):  $m/z$  274 (M-H).

**5-Aceto-6-methyl 4-(2-furyl)-2-oxo-1,2,3,4-tetrahydropyridimidine (4r).** <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$ =9.25 (s, 1H, NH), 7.70 (s, 1H, NH), 7.56 (dd, 1H<sub>arom</sub>, J=1.8, 0.9 Hz), 6.35 (dd, 1H<sub>arom</sub>, J=1.8, 3.0 Hz), 6.09 (d, 1H<sub>arom</sub>, J=3.3 Hz), 5.20 (d, 1H,

J=3.3 Hz, H-4), 2.27 (s, 3H, CH<sub>3</sub>), 2.05 (s, 3H, CH<sub>3</sub>).

Mass (ES/MS):  $m/z$  219 (M-H).

**Ethyl 6-methyl-2-thio-4-phenyl-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4s).** <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$ =9.19 (s, 1H, NH), 7.73 (s, 1H, NH), 7.22 (m, 5H<sub>arom</sub>), 5.14 (d, 1H, J=3.6 Hz, H-4), 3.40 (q, 2h, J=6.9 Hz, OCH<sub>2</sub>), 2.24 (s, 3H, CH<sub>3</sub>), 1.09 (t, 3H, J=6.9 Hz, CH<sub>3</sub>).

Mass (ES/MS):  $m/z$  275 (M-H).

**Acknowledgement.** The authors are thankful to the Head of Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University for providing laboratory facility.

Надійшла до редакції 03.03.2006 р.

### Хлорсульфонова кислота як каталізатор високоефективного твердофазного синтезу 3,4-дигідропіримідин-2(1H)-онів і -тієнів

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**Резюме.** Хлорсульфонову кислоту (ClSO<sub>3</sub>H) використовували як альтернативу традиційному кислому каталізу в реакції Бігінеллі між альдегідами, 1,3-дикарбонільними сполуками та сечовиною чи тиосечовиною. Описаний метод дає змогу швидко одержати дигідропіримідини з високим виходом в умовах твердофазного синтезу.

**Ключові слова:** ClSO<sub>3</sub>H каталіз, реакція Бігінеллі.

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