SHORT PAPER

J. Chem. Research (S),
2002, 436–438

Samarium chloride catalysed Biginelli reaction: one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

Xuesen Fan[a,c], Xinying Zhang[c] and Yongmin Zhang[a,b,*]

[a]*Department of Chemistry, Zhejiang University, Xixi Campus, Hangzhou 310028, P.R. China*

[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P.R. China*

[c]*Department of Chemistry, Henan Normal University, Xinxiang 453002, P.R. China*

An efficient synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives using samarium chloride as a catalyst from aldehyde, β-keto ester and urea or thiourea in ethanol is described; compared to the classical Biginelli method, this new method has the advantages of good yields and milder reaction conditions.

Keywords: samarium chloride, Biginelli reaction, 3,4-dihydropyrimidin-2(1*H*)-ones

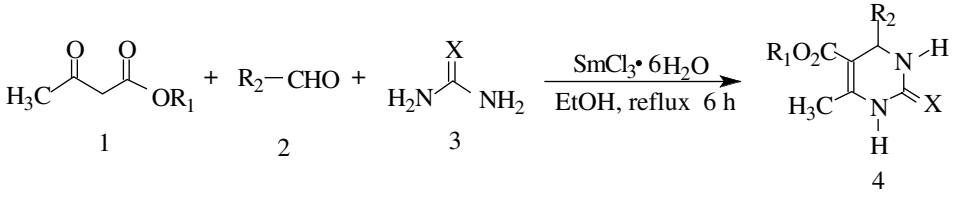
3,4-Dihydropyrimidin-2(1*H*)-one derivatives have attracted considerable interest in recent times because of their promising activities as calcium channel blockers, antihypertensive agents and α–1a-antagonists.[1] Moreover, several alkaloids containing the dihydropyrimidine unit which also exhibit interesting biological properties,[2] have been isolated from marine sources. Therefore, many synthetic methods for preparing such compounds have been developed.[3] The most simple and straightforward procedure, reported by Biginelli in 1893, involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea with catalytic amount of acid in a protic solvent.[4] However, this one-pot, one-step protocol often provides only low to moderate yields of the desired target molecules, in particular when substituted aromatic or aliphatic aldehydes are employed. Improvements in such synthesis have been sought continually, especially in recent years. Lewis acids (such as $BF_3 \cdot OEt_2$) in combination with transition metals and a proper proton source are effective catalysts for this reaction.[5] A polyphosphate ester was claimed to greatly improve the yield of the process.[6] Recently, it was reported that the acidic clay montmorillonite KSF could catalyse this reaction.[7] More recently, lanthanide triflate,[8] lanthanum chloride,[9] and indium chloride[10] were also reported as catalysts for one-pot syntheses of dihydropyrimidinones.

During recent years, the use of lanthanide(III) compounds as catalysts or promoters in organic synthesis has attracted great interest from many chemists.[11] For example, lanthanide trichloride was used in combination with $NaBH_4$,[12] $LiAlH_4$,[13] or Grignard reagent[14] for selective reduction or alkylation of carbonyl compounds. Fukuzawa reported that CeI_3 or $CeCl_3$/NaI could promote the aldol type reaction of α-haloketones and aldehydes to give enones.[15] We found that a similar reaction could be efficiently promoted by SmI_3.[16] We also found that samarium(III) iodide could promote Michael addition of active methylene compounds to α, β-unsaturated esters to form δ-carbonyl esters,[17] and the condensation of α-diketones or a-ketoesters with aldehydes to form benzylidene-substituted α-diketones or α-ketoesters in fair yields.[18]

Herein we wish to report that $SmCl_3 \cdot 6H_2O$ can be utilised as a very efficient catalyst for three component coupling reactions of β-keto ester (**1**), aldehyde (**2**) and urea or thiourea (**3**) to afford 3,4-dihydropyrimidin-2(1*H*)-ones (**4**) in high yields (Scheme 1).

In a typical experimental procedure, a solution of β-keto ester, aldehyde and urea or thiourea in ethanol was heated under reflux in the presence of a catalytic amount of $SmCl_3 \cdot 6H_2O$ (20 mol%) and one drop of conc. HCl for a certain period of time as required to complete the reaction (TLC). The reaction mixture was then poured onto crushed ice and the solid product separated was filtered and recrystallised. The results are listed in Table 1.

From Table 1, we can see that both ethyl acetoacetate and methyl acetoacetate participated in this reaction readily. A variety of substituted aromatic aldehydes have been subjected to this condensation very efficiently. Thiourea has been used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones which are also of much interest with regard to biological activity.[3] Thus, variations in all three components have been accommodated comfortably. As for the amount of the catalyst, we found that about 20 mol % of $SmCl_3 \cdot 6H_2O$ in reflux ethanol is sufficient to push the reaction forward. Higher amounts of $SmCl_3 \cdot 6H_2O$ did not improve the result to a great extent. The yields are high regardless of the structural variations in β-keto ester, aldehyde and urea or thiourea.



Scheme 1

* To receive any correspondence. E-mail: yminzhang@mail.hz.zj.cn

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Dihydropyrimidinones synthesized using new condition versus classical Biginelli conditions

Product	X	R^1	R^2	Isolated yield (%)	
				A[a]	B[b]
4a	O	Et	C6H5	91	789
4b	O	Et	4-(CH_3)-C_6H_4	89	69[c]
4c	O	Et	4-(CH_3O)-C_6H_4	90	619
4d	O	Et	4-(NO2)-C_6H_4	78	589
4e	O	Et	3-(Br)-C_6H_4	75	58[c]
4f	O	Et	4-(Cl)-C_6H_4	84	569
4g	O	Me	C_6H_5	93	429
4h	O	Me	4-(CH_3)-C_6H_4	87	40[c]
4l	O	Me	4-(CH_3O)-C_6H_4	85	289
4j	O	Me	4-(NO2)-C_6H_4	72	419
4k	O	Me	3-(Br)-C_6H_4	75	49[c]
4l	O	Me	4-(Cl)-C_6H_4	85	569
4m	S	Et	C_6H_5	78	709
4n	S	Me	4-(CH_3)-C_6H_4	74	57[c]
4o	S	Me	3-(Br)-C_6H_4	70	51[c]

[a]Method A: new reaction conditions (20mol% $SmCl_3.6H_2O$/HCl in EtOH, reflux 6h).

[b]Method B: classical Biginelli conditions (cat. HCl in EtOH reflux 18h).[9]

[c]This work.

Although the detailed mechanism of the above reaction has not been clarified yet, it is proposed that 3,4-dihydropyrimidin-2(1*H*)-one derivatives (**4**) may be formed through the usual mechanism proposed in the literature[5] (Scheme 2), in which the first step, the acid-catalyzed formation of an acyl imine intermediate (**5**) formed by reaction of the aldehyde (**2**) with urea or thiourea (**3**), is the key rate-limiting step. Interception of the iminium ion by ethyl or methyl acetoacetate (**1**) produces an open-chain ureide (**6**) which subsequently cyclises to the 3,4-dihydropyrimidin-2(1*H*)-one (**4**). Due to the empty orbital in the samarium ion, a complex of **1** and **6** with samarium(III) may be formed through a coordinative bond and so be stabilised by samarium.

In conclusion, the present procedure of the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by $SmCl_3{\cdot}6H_2O$ catalysed condensation of β-keto ester, aldehyde and urea or thiourea provides an efficient and much improved modification of Biginelli's reaction. With its simplicity and milder reaction conditions, this procedure will offer an easy access to substituted dihydropyrimidin-2(1H)-ones and thiones with varied substitution patterns in very high yields.

Experimental

General experimental details: Melting points were obtained on an electrothermal melting point apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker AC-400 (400 MHz) spectrometer using DMSO-d_6 solutions. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal TMS. Mass spectra were recorded on a HP 5989B MS spectrometer. Elemental analyses were performed on an EA-1110 instrument.

General procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-ones (**4**)*:* A solution of β–keto ester (**1**, 5mmol), aldehyde (**2**, 5 mmol), urea or thiourea (**3**, 10 mmol), $SmCl_3{\cdot}6H_2O$ (1mmol) and conc. HCl (one drop) in EtOH (15 ml) was heated under reflux for 6h. After cooling, the reaction mixture was poured onto crushed ice. The solid products were filtered off, washed with cold water and subsequently dried. All the products were characterised by their IR, ^{1}H NMR and MS spectral data (elemental analysis results are also provided for all the new compounds).

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**4a**): m.p. 201–203°C (lit.[5], 202–204°C); IR 3248, 3147, 1718, 1697, 1611 cm^{-1}; ^{1}H NMR δ 9.19 (br s, 1H), 7.73 (br s, 1H), 7.23–7.34 (m, 5H), 5.14 (d, *J* = 2.8 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.09 (t, *J* = 7.2, 3H).

5-(Ethoxycarbonyl)-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (**4b**): m.p. 214–216°C; IR 3269, 3172, 1708, 1687, 1638cm^{-1}; ^{1}H NMR δ 9.16 (br s, 1H), 7.69 (br s, 1H), 7.12 (m, 4H), 5.10 (d, *J* = 2.8 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 1.10 (t, *J* = 7.2, 3H); MS: m/z (%): 274 (M, 19), 245 (88), 201 (60), 183 (100), 137(54). Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.54; H, 6.68; N, 10.30%.

5-(Ethoxycarbonyl)-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**4c**): m.p. 198–200°C (lit.[5], 201–203°C); IR 3239, 3124, 1710, 1704, 1647cm^{-1}; ^{1}H NMR δ 9.12 (br s, 1H), 7.98 (br s, 1H), 7.12–6.93 (m, 4H), 5.11 (d, *J* = 2.8 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.65 (s, 3H), 2.25 (s, 3H), 1.09 (t, *J* = 7.2, 3H).

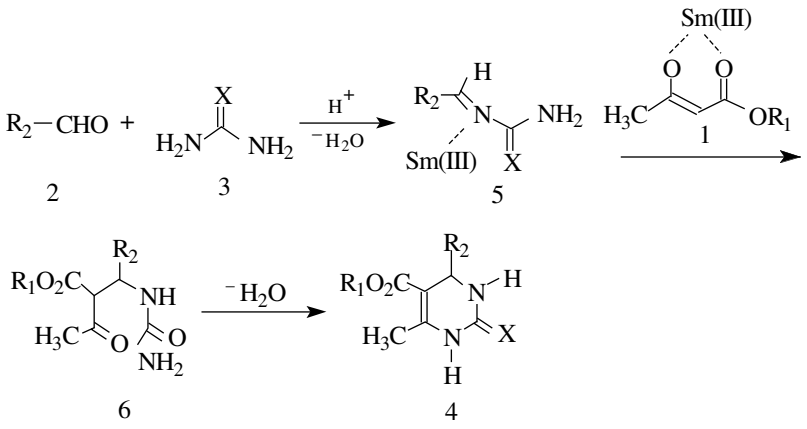
5-(Ethoxycarbonyl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4d**): m.p. 207–209°C (lit.[5], 208–211°C); IR 3244, 3018, 1712, 1690, 1635 cm^{-1}; ^{1}H NMR δ 9.35 (br s, 1H), 8.23 (d, *J* = 8.5 Hz), 7.86 (br s, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 5.24 (d, *J* = 2.8 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.10 (t, *J* = 7.2, 3H).

5-(Ethoxycarbonyl)-6-methyl-4-(3-bromophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4e**): m.p. 183–185°C (lit.[19], 185–186°C); IR 3241, 3122, 1711, 1673, 1621 cm^{-1}; ^{1}H NMR δ 9.25 (br s, 1H), 7.78 (br s, 1H), 7.25–7.36 (m, 4H), 5.16 (d, *J* = 2.8 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.09 (t, *J* = 7.2, 3H).

5-(Ethoxycarbonyl)-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4f**): m.p. 211–214°C (lit.[5], 213–215°C); IR 3243, 3092, 1709, 1668, 1615 cm^{-1}; ^{1}H NMR δ 9.21 (br s, 1H), 7.76 (br s, 1H), 7.26–7.41 (m, 4H), 5.15 (d, *J* = 2.8 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.09 (t, *J* = 7.2, 3H).

5-(Methoxycarbonyl)-6-methyl-4-phenym-3,4-dihydropyrimidin-2(1H)-one (**4g**): m.p. 206–209°C (lit.[5], 209–212°C); IR 3328, 3015, 1702, 1684, 1621 cm^{-1}; ^{1}H NMR δ 9.22 (br s, 1H), 7.75 (br s, 1H), 7.26–7.37 (m, 5H), 5.15 (d, *J* = 2.8 Hz, 1H), 3.58 (s, 3H), 2.25 (s, 3H).

5-(Methoxycarbonyl)-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (**4h**): m.p. 202–204°C; IR 3228, 2980, 1705, 1650, 1610 cm^{-1}; ^{1}H NMR δ 9.18 (br s, 1H), 7.70 (br s, 1H), 7.11 (m, 4H), 5.10 (d, *J* = 2.8 Hz, 1H), 3.52 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H); MS: *m/z* (%): 260 (M, 18), 245 (44), 169 (100), 137 (71). Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.74; H, 6.34; N, 10.58%.



Scheme 2

5-(Methoxycarbonyl)-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**4i**): m.p. 190–193°C (lit.[5], 192–194°C); IR 3234, 3100, 1698, 1657, 1608 cm^{-1}; ^1H NMR δ 9.16 (br s, 1H), 7.71 (br s, 1H), 7.13–6.87 (m, 4H), 5.10 (d, *J* = 2.8 Hz, 1H), 3.78 (s, 3H), 3.48 (s, 3H), 2.28 (s, 3H).

5-(Methoxycarbonyl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4j**): m.p. 233–236°C (lit.[5], 235–237°C); IR 3250, 2980, 1715, 1670, 1626 cm^{-1}; ^1H NMR δ 9.35 (br s, 1H), 8.20 (d, *J* = 8.7 Hz, 2H), 7.88 (br s, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 5.28 (d, *J* = 2.8 Hz, 1H), 3.49 (s, 1H), 2.25 (s, 3H).

5-(Methoxycarbonyl)-6-methyl-4-(3-bromophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4k**): m.p. 229–231°C; IR 3230, 33026, 1701, 1650, 1610 cm^{-1}; ^1H NMR δ 9.30 (br s, 1H), 7.81 (br s, 1H), 7.21–7.46 (m, 4H), 5.14 (d, *J* = 2.8 Hz, 1H), 3.54 (s, 3H), 2.26 (s, 3H); MS: *m*/*z* (%): 326 (M+2, 3), 324 (M, 3), 169 (100), 137(51). Anal. Calcd. for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; N, 8.62. Found: C, 48.15; H, 3.98; N, 8.54%.

5-(Methoxycarbonyl)-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4l**): m.p. 202–205°C (lit.[5], 204–207°C); IR 3238, 3117, 1708, 1648, 1601 cm^{-1}; ^1H NMR δ 9.28 (br s, 1H), 7.78 (br s, 1H), 7.23–7.36 (m, 5H), 5.14 (d, *J* = 2.8 Hz, 1H), 3.54 (s, 3H), 2.25 (s, 3H).

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (**4m**): m.p. 197–199°C (lit.[20], 199–200°C); IR 3280, 3010, 1700, 1660, 1600 cm^{-1}; ^1H NMR δ 10.22 (br s, 1H), 9.41 (br s, 1H), 7.12–7.25 (m, 5H), 5.24 (d, *J* = 2.8 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.12 (t, *J* = 7.2, 3H).

5-(Methoxycarbonyl)-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-thione (**4n**): m.p. 158–161°C; IR 3250, 2997, 1700, 1638, 1612 cm^{-1}; ^1H NMR δ 10.32 (br s, 1H), 9.63 (br s, 1H), 7.08–7.15 (m, 4H), 5.13 (d, *J* = 3.2 Hz, 1H), 3.55 (s, 1H), 2.28 (s, 3H), 2.26 (s, 3H); MS: *m*/*z* (%): 276 (M, 82), 261 (53), 217(46), 185 (100), 153(21). Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.66; H, 6.02; N, 10.15%.

5-(Methoxycarbonyl)-6-methyl-4-(3-bromophenyl)-3,4-dihydropyrimidin-2(1H)-thione (**4o**): m.p. 232–236°C; IR 3268, 3052, 1702, 1670, 1621 cm^{-1}; ^1H NMR δ 10.44 (br s, 1H), 9.70 (br s, 1H), 7.20–7.50 (m, 4H), 5.18 (d, *J* = 3.2 Hz, 1H), 3.56 (s, 3H), 2.30 (s, 3H); MS: *m*/*z* (%): 342 (M+2, 20), 340 (M, 20), 185 (100), 153(32). Anal. Calcd. for $C_{13}H_{13}BrN_2O_2S$: C, 45.76; H, 3.84; N, 8.21. Found: C, 45.64; H, 3.79; N, 8.24%.

We are grateful to the National Natural Science Foundation of China (Project No. 20072033) and the NSF of Zhejiang province for financial support.

Received 3 December 2001; accepted 10 March 2002
Paper 01/1168

References

1 K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg and B.C. O'Reilly, *J. Med. Chem.*, 1991, **34**, 806 and references cited therein.
2 L.E. Overman, M. H. Rabinowitz and P.A. Renhowe, *J. Am. Chem. Soc.*, 1995, **117**, 2657.
3 (a) C.O. Kappe, *Tetrahedron*, 1993, **49**, 6937; (b) K.S. Atwal, B.C. O'Reilly, J.Z. Gougoutas and M.F. Malley, *Heterocycles*, 1987, **26**, 1189; (c) H. Bohme and E. Mundlos, *Chem. Ber.*, 1953, **86**, 1414; (d) J.D. Fissekis and F. Sweet, *J. Org. Chem.*, 1973, **38**, 1963; (e) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.*, 1964, **12**, 804; (f) J. Barluenga, M. Tomas, V. Rubio and V. Gotor, *J. Chem. Commun.*, **1979**, 675.
4 P. Biginelli, *Gazz. Chim. Ital.,* 1893, **23**, 360.
5 E.H. Hu, D.R. Sidler and U.-H. Dolling, *J. Org. Chem.*, 1998, **63**, 3454.
6 C.O. Kappe and S.F. Falsone, *Synlett*, 1998, 718.
7 F. Bigi, S. Carloni, B. Frullanti, R. Maggi and G. Sartori, *Tetrahedron Lett.*, 1999, **40**, 3465.
8 Y. Ma, C. Qian, L. Wang and M. Yang, *J. Org. Chem.*, 2000, **65**, 3864.
9 J. Lu, Y. Bai, Z. Wang, B. Yang and H. Ma, *Tetrahedron Lett.*, 2000, **41**, 9075.
10 B.C. Ranu, A. Hajra and U. Jana, *J. Org. Chem.*, 2000, **65**, 6270.
11 (a) T. Imamoto, In *Lanthanides in Organic Synthesis*. Academic Press: New York, 1994; (b) S. Kobayashi, *Synlett*, 1994, 689; (c) G.A. Molander, *Chem. Rev.*, 1992, **92**, 29.
12 J.L. Luche and S.L. Gemal, *J. Am. Chem. Soc.*, 1979, **101**, 5848.
13 S. Fukuzawa, T. Fujinami, S. Yamauchi and S. Sakai, *J. Chem. Soc., Perkin Trans. 1,* **1986**, 1929.
14 T. Imamoto, N. Takiyama and K. Nakamura, *Tetrahedron Lett.*, 1985, **26**, 4763.
15 S. Fukuzawa, T. Tsuruta and S. Sakai, *J. Chem. Soc., Perkin Trans. 1,* **1986**, 1473.
16 Y.P. Yu, R.H. Lin and Y.M. Zhang, *Tetrahedron Lett.*, 1993, **34**, 4547.
17 X.Y. Chen, W.L. Bao and Y.M. Zhang, *Chin. Chem. Lett.*, 2000, **11**, 483.
18 W.L. Bao and Y.M. Zhang, *Synth. Commun.*, 1996, **26**, 3025.
19 J. Lu and H.R. Ma, *Chin. J. Org. Chem.*, 2000, **20**, 815.
20 M.S. Akhtar, M. Seth and A.P. Bhaduri, *Ind. J. Chem.,* 1987, **26B**, 556.