SHORT PAPER

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One-pot construction 3,4-dihydropyrimidin-2(1*H*)-ones catalysed by samarium(III)†

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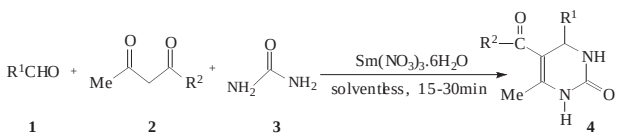
An efficient synthesis of dihydropyrimidin-2(1*H*)-ones using samarium(III) nitrate hexahydrate as a catalyst from an aldehyde, 1,3-dicarbonyl compounds and urea under solventless conditions is described. Compared with the classical Biginelli reaction, the yields of this protocol increased from 20–50% to 78–98% while the reaction time was significantly shortened from 18 h to 15–30 min.

Keywords: Biginelli reaction; 3,4-dihydropyrimidin-2(1*H*)-ones; solvent-free; samarium(III) nitrate hexahydrate, synthesis

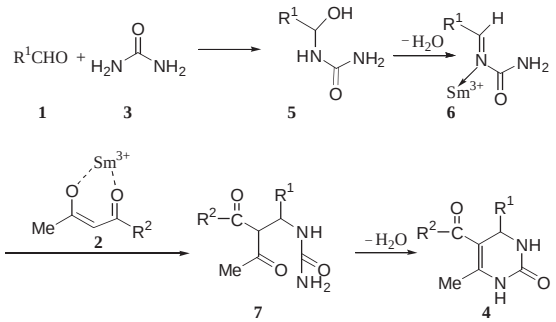
The classical Biginelli reaction, first described in 1893 , was a one-pot condensation using β-dicarbonyl compounds with aldehydes (aromatic and aliphatic aldehydes) and urea or thiourea in ethanol solution containing catalytic amounts of acid[1] to afford dihydropyrimidinones which exhibit important pharmacological properties (*i.e.* calcium channel blockers, antihypertensive agents and α-1a-antagonists.)[2] This method, however, involves long reaction time, harsh reaction conditions and unsatisfactory yields.Therefore, the discovery of milder and practical routes for the synthesis of dihydropyrimidin-2(1*H*)-ones by the Biginelli reaction continues to attract the attention of researchers. Recently, $BF_3{\cdot}OEt_2$,[3] polyphosphate ester (PPE),[4] KSF clay,[5] indium chloride,[6] ferric chloride hexahydrate,[7] lanthanum chloride,[8] and lanthanide triflate[9] are found to be effective for this transformation. More recently, several other conditions for the one-pot synthesis of dihydropyrimidinones have also been reported.[10-16] However, many of these one-pot procedures generally employ strong protic or Lewis acids, prolonged reaction time, hazardous reagents (such as acetonitrile) and high temperature. Meanwhile, environmental concerns in chemical research and industry are ever increasing. The possibility of performing multicomponent reactions under solventless conditions could enhance their efficiency from an economic as well as an ecological point of view, so solvent-free chemical synthesis has recently received much attention.[17] Consequently, there is scope for further improvement toward milder reaction conditions, and better yields.



Scheme 1

In recent years, Sm(III) has been used as an efficient Lewis acid for various transformation such as carbon–carbon double bond formation,[18] aldol condensation,[19] β-diketone and α-Selenoketones synthesis.[20-21] In this paper we report a general and practical route for the Biginelli cyclocondensation reaction using Sm(III) as the catalyst under solvent-free conditions as shown in Scheme 1. This is a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields of the dihydropyrimidin-2(1*H*)-ones and greatly decreases environmental pollution. In the presence of $Sm(NO_3)_3{\cdot}6H_2O$ (0.3 mmol), the reaction of benzaldehyde (**1a,** 1 mmol), ethyl acetoacetate (**2a**,1 mmol), and urea (**3** ,1.5 mmol) was carried out in a one-pot condensation under solvent-free conditions for 20 min, and resulted in formation of 4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**) in 92% yield. A wide range of structurally varied 1,3-dicarbonyl compounds, aldehydes and urea proceeded smoothly and were very fast to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in high yields as listed in Table 1. Many pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdraw substituents all reacted very well, giving moderate to excellent yields. Moreover, when aliphatic aldehydes, 1,3-dicarbonyl compounds, and urea reacted under solventless conditions and catalysed by Sm(III), the corresponding dihydropyrimidinones were also provided in high yields.

We propose a mechanism of the Sm(III)-catalysed reaction as shown in Scheme 2. Aldehyde reacts with urea to form an acyl imine intermediate **6** which is activated by Sm(III). Subsequent addition of the β-carbonyl compound followed by cyclisation and dehydration affords the dihydropyrimidinones.



Scheme 2

In conclusion, we have developed a novel and simple modification of the Biginelli dihydropyrimidine reaction. By using $Sm(NO_3)_3{\cdot}6H_2O$ as the catalyst under solvent-free conditions from readily available starting materials, the yields can be increased from 20–50% to 78–98% while the reaction time was shortened from 18 h to 15–30 min. Therefore, this Sm(III)-catalysed Biginelli reaction is a simple, high-yielding, timesaving, and environmentally friendly protocol, which make it an important alternative to the classical acid-catalysed Biginelli reaction.

Experimental

Melting points were determined by using a Yanaco micro melting point apparatus and were not corrected. IR spectra were recorded on a Bruker Vector 22 spectrophoto-meter using KBr pellets for solids.

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

Table 1 Sm(III)-catalysed synthesis of dihydropyrimidin-2(1*H*)-ones[a]

DHPM	R^1	R^2	Time/min	Yield/%[b]	m.p./°C[c]	
4a	C_6H_5	OEt	20	92	205–206	203–205[11]
4b	3-(NO_2)–C_6H_4	OEt	30	84	228–230	227–228[11]
4c	4-(OMe)–C_6H_4	OEt	20	97	202–204	201–202[16]
4d	4-(NO_2)–C_6H_4	OEt	20	90	209–212	207–210[9]
4e	2-(Cl)–C_6H_4	OEt	25	89	214–216	214-215[11]
4f	CH_3CH_2	OEt	15	90	179–181	___
4g	$(CH_3)_2CHCH_2$	OEt	25	84	185–186	___
4h	3-(NO_2)–C_6H_4	OMe	20	88	240–241(dec)	___
4i	C_6H_5	OMe	20	94	210–213	209–216[3]
4j	4-(NO_2)–C_6H_4	OMe	30	88	237–239	235–237[9]
4k	2-(Cl)–C_6H_4	OMe	15	87	226–229	___
4l	CH_3CH_2	OMe	20	89	184–185	___
4m	$CH_3CH_2CH_2$	OMe	30	98	174–175	___
4n	$(CH_3)_2CHCH_2$	OMe	15	87	178–179	___
4o	4-(OMe)–C_6H_4	OMe	15	96	194–196	191–193[9]
4p	4-(NO_2)–C_6H_4	Me	20	96	231–232(dec)	230(dec)[9]
4q	3-(NO_2)–C_6H_4	Me	20	92	268–270(dec)	___
4r	$CH_3CH_2CH_2$	Me	30	78	151–152	___
4s	C_6H_5	Me	15	98	235–236	233–236[9]

[a]All products were characterised by ^{1}H NMR, ^{13}C NMR, IR and mass spectra. [b]Isolated yields. [c]Melting points were uncorrected.

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM -400 MHz or AM-500 Mhz spectrometer using DMSO-d_6 as the solvent and using TMS as internal standard. Mass spectra were obtained on an HP 5989B MS spectrometer at an ionisation potential of 70 eV.

General procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-ones **4**: Aldehyde (**1**, 1 mmol), 1,3-dicarbonyl compound (**2**, 1.5 mmol), urea (**3**, 1.5 mmol) and $Sm(NO_3)_3{\cdot}6H_2O$ (133.4 mg, 0.3 mmol) were heated at 100°C under stirring for 15–30 min as shown in Table 1. Then water was added, and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was washed with ether, and then recrystallised from ethanol to afford the product **4**.

5-Ethoxycarbonyl-4-ethyl-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4f):** m.p. 179–181 °C; IR(KBr): 3250, 3123, 2962, 1723, 1703, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.82 (s, 1H, NH), 7.18 (s, 1H, NH), 4.03–4.09 (m, 3H, H–4 and O$\underline{CH_2}CH_3$), 2.16 (s, 3H, C_6–CH_3), 1.41 (m, 2H, $\underline{CH_2}CH_3$), 1.17 (t, *J*=6.0 Hz, 3H, $OCH_2\underline{CH_3}$), 0.78 (t, *J*=7.5 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR: δ 165.3, 152.6, 148.1, 98.7, 58.8, 51.2, 29.4, 17.5, 14.0, and 8.31; MS (70 eV, EI): *m/z* 212 (M^+,0.43%).

5-Ethoxycarbonyl-4-isobutyl-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4g):** m.p. 185–186 °C; IR(KBr): 3447, 3244, 3112, 2951, 1701, 1652 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.86 (s, 1H, NH), 7.32 (s, 1H, NH), 4.01–4.10 (m, 3H, H–4 and O$\underline{CH_2}CH_3$), 2.16 (s, 3H, C_6–CH_3), 1.69 (m, 1H, $\underline{CH_2}CH(CH_3)_2$), 1.35 (m, 1H, $\underline{CH_2}CH(CH_3)_2$), 1.17 (t, *J*=7.0 Hz, 3H, $OCH_2\underline{CH_3}$), 1.10 (m, 1H, $CH_2\underline{CH}(CH_3)_2$), 0.85 (d, *J*=6.5 Hz, 6H, $CH_2CH(\underline{CH_3})_2$) ; ^{13}C NMR: δ 165.1, 152.6, 147.9, 100.2, 58.8, 48.1, 45.8, 23.5, 22.7, 21.3, 17.4, 14.0; MS (70 eV, EI): *m/z* 241 (M^++1,1.08%).

5-Methoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4h):** m.p. 240–241°C (dec.); IR(KBr): 3358, 3244, 3102, 2957, 1701, 1641 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.31 (s, 1H, NH), 8.09–8.13 (m, 2H, Ar–H),7.85 (s, 1H, NH), 7.63–7.70 (m, 2H, Ar–H), 5.31 (d, *J*=3.0 Hz, 1H, H–4), 3.35 (s, 3H, $COOCH_3$), 2.28 (s, 3H, C_6–CH_3); ^{13}C NMR: δ 165.5, 151.7, 149.6, 147.8, 146.6, 132.8, 130.1, 122.3, 120.8, 98.0, 53.3, 50.8, 17.8; MS (70 eV, EI): *m/z* 291 (M^+, 5.86%).

5-Methoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4k):** m.p. 226–229 °C; IR(KBr): 3367, 3221, 3103, 2948, 1714, 1698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.21 (s, 1H, NH), 7.59 (s, 1H, NH), 7.25–7.40 (m, 4H, Ar–H), 5.62 (d, *J*=2.5 Hz, 1H, H–4), 3.45 (s, 3H, $COOCH_3$), 2.30 (s, 3H, C_6–CH_3); ^{13}C NMR: δ 165.4, 151.3, 149.3, 141.4, 131.6, 129.4, 129.0, 128.6, 127.6, 97.6, 51.3, 50.6, 17.6 ; MS (70 eV, EI): *m/z* 280 (M^+, 5.13%).

5-Methoxycarbonyl-4-ethyl-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4l):** m.p. 184–185 °C; IR(KBr): 3249, 3118, 2961, 1728, 1708, 1680cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.96 (s, 1H, NH), 7.30 (s, 1H, NH), 4.01 (m, 1H, H–4), 3.59 (s, 3H, $COOCH_3$), 2.16 (s, 3H, C_6–CH_3) 1.39 (q, *J*=7.5 Hz, 2H, $\underline{CH_2}CH_3$), 0.77 (t, *J*=7.5 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR: δ 165.9, 152.7, 148.6, 98.5, 51.3, 50.7, 29.5, 17.7, 8.4; MS (70 eV, EI): *m/z* 198 (M^+,0.59%).

5-Methoxycarbonyl-4-propyl-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4m):** m.p. 174–175 °C; IR(KBr): 3442, 3252, 3123, 2957, 1726, 1708, 1653 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ8.94(s, 1H, NH), 7.31 (s, 1H, NH), 4.03 (t, *J*=3.2Hz, 1H, H–4), 3.59 (s, 3H, $COOCH_3$), 2.15 (s, 3H, C_6–CH_3) 1.19–1.40 (m, 4H, $\underline{CH_2}CH_2CH_3$), 0.82 (t, *J*=6.7 Hz, 3H, $CH_2CH_2\underline{CH_3}$) ; ^{13}C NMR: δ 165.8, 152.6, 148.3, 99.1, 50.6, 49.8, 17.6, 16.9, 13.6; MS (70 eV, EI): *m/z* 212 (M^+,0.43%).

5-Methoxycarbonyl-4-isobutyl-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4n):** m.p. 178–179 °C; IR(KBr): 3442, 3252, 2957, 1726, 1708, 1653 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.88 (s, 1H, NH), 7.32 (s, 1H, NH), 4.03 (t, *J*=4.5Hz, 1H, H-4), 3.60 (s, 3H, $COOCH_3$), 2.16 (s, 3H, C_6–CH_3), 1.69 (m, 1H, $\underline{CH_2}CH(CH_3)_2$), 1.37 (m, 1H, $\underline{CH_2}CH(CH_3)_2$), 1.11 (m, 1H, $CH_2\underline{CH}(CH_3)_2$), 0.85 (m, 6H, $CH_2CH(\underline{CH_3})_2$) ; ^{13}C NMR: δ 165.7, 152.6, 148.0, 100.2, 50.5, 48.2, 45.8, 23.4, 22.7, 21.4, 17.5; MS (70 eV, EI): *m/z* 227 (M^++1,0.63%).

5-Aceto-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4q):** m.p. 268–270 °C (dec.); IR(KBr): 3349, 3273, 3062, 1715, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.33 (s, 1H, NH), 7.98 (s, 1H, NH), 7.61–8.12 (m, 4H, Ar–H), 5.40 (d, *J*=3.2 Hz, 1H, H–4), 2.32 (s, 3H, $COCH_3$), 2.19 (s, 3H, C_6–CH_3); ^{13}C NMR: δ 193.9, 151.9, 149.0, 147.8, 146.3, 132.9, 130.1, 122.2, 121.0, 109.4, 52.9, 30.5, 19.0; MS (70eV, EI): *m/z* 275 (M^+, 4.34%).

5-Aceto-4-propyl-6-methyl-3,4-dihydropyrimidi-2(1H)-one **(4r):** m.p. 151–152 °C; IR(KBr): 3247, 3113, 2956, 1723, 1625 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.94 (s, 1H, NH), 7.42 (s, 1H, NH), 4.09 (t, *J*=3.2 Hz, 1H, H–4), 2.18 (s, 3H, $COCH_3$), 2.16 (s, 3H, C_6-CH_3), 1.20 (m, 4H, $\underline{CH_2}CH_2CH_3$), 0.82 (t, *J*=7.0 Hz, 3H, $CH_2CH_2\underline{CH_3}$); ^{13}C NMR: δ 194.5, 153.3, 147.8, 111.1, 50.5, 30.6, 19.3, 17.6, 14.2; MS (70 eV, EI): *m/z* 196 (M^+, 1.27%).

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