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One-pot synthesis of dihydropyrimidiones catalyzed by strontium(II) triflate under solvent-free conditions

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Abstract—A simple, efficient and practical procedure for the Biginelli reaction using strontium(II) triflate [$Sr(OTf)_2$] as a novel catalyst is described under solvent-free conditions in high yields. The catalyst exhibited remarkable reactivity and it is reusable. Some of dihydropyrimidiones showed strong pesticidal activity.

Dihydropyrimidiones and their derivatives (denoted as Biginelli compounds) have attracted considerable interest because of their pharmaceutical and therapeutic properties,[1] such as antibacterial, antiviral, antitumour and anti-inflammatory activities. Some of them have been successfully used as calcium channel blockers, antihypertensive agents, α-1a-antagonists and neuropeptide Y (NPY) antagonists.[2] Moreover, several alkaloids containing the dihydropyrimidiones core unit have been isolated from marine source, which also shows interesting biological properties.[3] Among these most notably are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.[4] Therefore, preparation of this heterocyclic nucleus has gained great importance in organic synthesis.

The simple and direct method for the synthesis of dihydropyrimidiones was first reported by Biginelli in 1893, involving a one-pot condensation of an aldehyde, β-ketoester and urea under strongly acidic conditions. However it suffers from low yields (20–50%) of products in the cases of substituted aromatic and aliphatic aldehydes.[1a] This has led to the development of multistep of synthetic strategies that produce somewhat better yields but lack the simplicity of one-pot, one-step synthesis.[1c,5]

In order to improve the efficiency of Biginelli reaction, the use of a number of Lewis acid catalysts, such as LiBr,[6] $FeCl_3{\cdot}6H_2O$,[7] $BF_3{\cdot}OEt_2$,[8] $ZrCl_4$,[9] $BiCl_3$,[10] $Mn(OAc)_3{\cdot}2H_2O$,[11] $LaCl_3{\cdot}H_2O$,[12] $InCl_3$,[13] $Cu(OTf)_2$,[14] $In(OTf)_3$,[15] lanthanide triflates,[16] $ZnCl_2$,[17] $FeCl_3{\cdot}6H_2O$ and $NiCl_2{\cdot}6H_2O$,[18] $MgBr_2$,[19] $CeCl_3{\cdot}7H_2O$,[20] have been reported subsequently. In addition, significant rate and yield enhancement were reported for Biginelli reaction carried out under microware irradiation.[21] In recent years, several other conditions for the one-pot preparation dihydropyrimidiones have also been reported.[22] However, many of these procedures require strongly acidic conditions. As increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that can avoid using harmful organic solvents, or even better, do not need solvents at all. Recently, metal triflate salts were widely used in organic synthesis[23] due to their low toxicity, low cost, high stability, ease of handling and recoverable from water. However, up to now, $Sr(OTf)_2$ has not been carefully studied as a catalyst. Judging from these unique properties of these metal triflate salts, we would like to report a simple, efficient and practical method for the synthesis of dihydropyrimidiones using $Sr(OTf)_2$[24] as catalyst in solvent-free conditions (Scheme 1).

In a typical experiment, a mixture of an aldehyde, β-diketoester, urea or thiourea in solvent-free was heated at 70 °C in the presence of catalytic amount of $Sr(OTf)_2$ (1 mol %) for 4 h. The reaction was monitored

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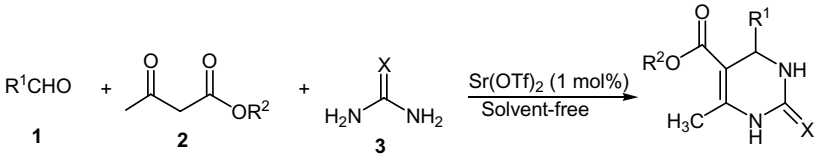


Scheme 1.

by TLC. Then the reaction mixture was poured into cold water and stirred for 5 min, and the solid product was obtained by simple filtration in high yields.

Table 1. $Sr(OTf)_2$-catalyzed condensation of benzaldehyde, ethyl acetate and urea under different reaction conditions[a]

Entry	Solvent	Catalyst (mol %)	Yield of **4a** (%)[b]
1	Toluene	1	70
2	Benzene	1	58
3	Cyclohexane	1	92
4[c]	CH_2Cl_2	1	94
5	CH_3CH_2OH	1	95
6	CH_3CN	1	98
7	H_2O	1	21
8[d]	None	1	97, 94, 92, 93, 92
9	None	5	96
10	None	0.2	73

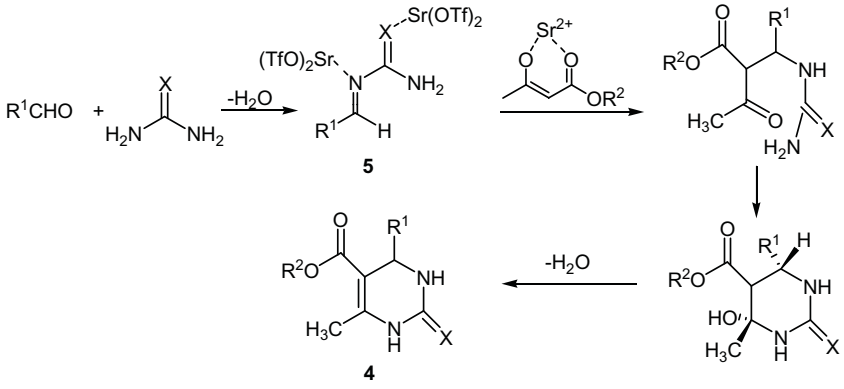
[a] The reaction were carried out in the presence of benzaldehyde (5 mmol), ethyl acetate (5 mmol), urea (7.5 mmol) and $Sr(OTf)_2$ in solvent (25 mL, entries 1–7) at 70 °C for 4 h.
[b] Isolated yield.
[c] Reflux temperature.
[d] Catalyst was reused for five times.

A series of reaction conditions using $Sr(OTf)_2$ as a catalyst were examined when the substrates are benzaldehyde, ethyl acetoacetate and urea. The results are summarized in Table 1. We found that Biginelli reaction is affected by various solvents from Table 1. The results indicate that toluene and benzene are unsuitable for the reaction. Solvents such as cyclohexane, dichloromethane, ethanol and acetonitrile, proved to be effective. Low chemical yield was obtained (21%) when H_2O was used as solvent. Most excitingly, the Biginelli reaction could be also carried out under solvent-free condition in excellent yield (97%). Moreover, our study showed the best results were observed when the molar ratio of aldehyde **1**, β-diketoester **2** and urea **3** was 1:1:1.5. In addition, we found that the yields were not obviously affected with different amount of $Sr(OTf)_2$. One mole percent of $Sr(OTf)_2$ was sufficient and excessive amount of catalyst did not increase the yieldssignificantly (entries 8–10). The activity of the recycled $Sr(OTf)_2$ were also examined according to the typical experiment conditions. We obtained desired product in 97%, 94%, 92%, 93% and 92% yields after 1–5 runs, respectively (entry 8).

Table 2. Strontium triflate-catalyzed synthesis of dihydropyrimidinones under solvent-free conditions[a]

Entry	R^1	R^2	X	Yield[b] (%)	Mp (°C)[c] found	Mp (°C) reported
4a	C_6H_5	C_2H_5	O	97	206–208	209–210[17]
4b	3-$O_2NC_6H_4$	C_2H_5	O	94	230–232	231–235[17]
4c	4-HOC_6H_4	C_2H_5	O	88	237–238	236–238[17]
4d	3-$CH_3OC_6H_4$	C_2H_5	O	94	206–208	207–208[13]
4e	4-$Me_2NC_6H_4$	C_2H_5	O	93	253–254	256–258[18]
4f	3-CH_3O–4-HO–C_6H_3	C_2H_5	O	95	235–236	231–232[18]
4g	2-ClC_6H_4	C_2H_5	O	88	220–221	222–223[17]
4h	4-ClC_6H_4	C_2H_5	O	95	215–216	216–217[17]
4i	2-Furyl	C_2H_5	O	90	208–210	208–210[17]
4j	4-$O_2NC_6H_4$	C_2H_5	O	98	211–213	212–214[17]
4k	4-$CH_3C_6H_4$	C_2H_5	O	87	205–206	169–171[9]
4l	C_6H_5	CH_3	O	93	212–213	209–212[8]
4m	3-$O_2NC_6H_4$	CH_3	O	93	273–275	>250[19]
4n	4-$Me_2NC_6H_4$	CH_3	O	90	213–215	213–215[20]
4o	3-OCH_3–4-HO–C_6H_3	CH_3	O	85	253–254	—
4p	3-OCH_3–4-HO–5-NO_2–C_6H_2	CH_3	O	88	248–249	—
4q	4-ClC_6H_4	CH_3	O	93	206–208	204–207[8]
4r	3-$CH_3OC_6H_4$	CH_3	O	89	213–214	—-
4s	C_6H_5	C_2H_5	S	92	207–208	208–209[15]
4t	3-$O_2NC_6H_4$	C_2H_5	S	92	206–207	206–207[16b]
4u	4-ClC_6H_4	C_2H_5	S	93	208–210	209–210[16b]
4v	4-$Me_2NC_6H_4$	C_2H_5	S	86	209–210	—
4w	4-HOC_6H_4	C_2H_5	S	87	202–203	198–200[9]
4x	4-$CH_3C_6H_4$	C_2H_5	S	92	214–215	192–194[13]

[a] Reaction conditions: aldehyde **1** (5 mmol), β-diketoeaster **2** (5 mmol), urea or thiourea **3** (7.5 mmol) and $Sr(OTf)_2$ (0.25 mmol), 70 °C, 4 h.
[b] Isolated yield.
[c] Melting points were uncorrected.



Scheme 2.

In order to study the generality of this procedure, a series of Biginelli compounds were synthesized with similar operations. The results were listed in Table 2. The three-component condensation reactions proceeded smoothly at 70 °C and were complete in 4 h under these conditions. The yields were significantly increased from 20–50% of the classical Biginelli method to 87–98%, and the reaction time shortened from 18 to 4 h. A variety of substituted aromatic aldehydes, bearing either electron-donating or electron-withdrawing substituents, afforded high yields of the products in high yields and high purities (monitored by ^{1}H NMR). Acid sensitive aldehydes such as furfural worked well without the formation of any side products and afforded the desired products in 90% yield (entry **4i**). Furthermore, thiourea has been used with similar success to provided the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones, which are also of interest with regard to their biological activities.[1b] Using methyl acetoacetate instead of ethyl acetoacetate, the desired products were also obtained in high yields (entries **4l**–**r**). In continuation of our interest in the studies of bioactivity of pesticides,[25] we studied the bioactivity of these type compounds. To our excitement, the preliminary bioassay showed that 3,4-dihydropyrimidin-2(1*H*)-thiones had strong biological activity. Especially, **4t** exhibited 100% inhibition against *Spodoptera eridania* at 500 ppm after 24 h.

This reaction may proceed via acyl imine intermediate[16a] **5**, formed by the reaction of the aldehyde and urea and stabilized by $Sr(OTf)_2$. Subsequent addition of β-diketo-easter enolate to the acylimine, followed by cyclization and dehydration, afforded the corresponding dihydropyrimidiones (Scheme 2).

In conclusion, we have described a simple and general method for the synthesis of dihydropyrimidiones by using a reusable $Sr(OTf)_2$.[26] The method offers several advantages including high yields, environmental friendly procedure, short reaction times, simple work up procedure and easy isolation, which make it a useful process for the synthesis of dihydropyrimidiones as well as the thio-derivatives. Hence, it is a useful addition to the existing methods.

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26. General procedures for one-pot preparation of 3,4-dihydropyrimidiones or its derivatives **4** using $Sr(OTf)_2$ as a catalyst: A mixture of aldehyde (5 mmol), β-diketoester (5 mmol) and urea or thiourea (7.5 mmol) and $Sr(OTf)_2$ (0.05 mmol) was heated at 70 °C under stirring for 4 h. After cooling, the reaction mixture was poured into cold water and stirred for 5 min. The solid was suction filtered, washed with cold water (20 mL × 2), filtered and recrystallized from ethyl acetate or ethanol to afford pure product. Selected physical data for compounds:
Methyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4o**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H, NH), 8.91 (s, 1H, OH), 7.64 (s, 1H, NH), 6.81 (s, 1H, ArH), 6.69 (d, 2H, $J = 8.0$ Hz, ArH), 6.59 (d, 1H, $J = 8.0$ Hz, ArH), 5.06 (s, 1H, CH), 3.73 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 152.2, 148.2, 147.3, 145.8, 135.6, 118.1, 115.2, 110.8, 99.2, 55.5, 53.4, 50.7, 17.7. IR (KBr): 3396, 3116, 3260, 2955, 1679, 1649, 1519 cm^{-1}. MS (ESI): *m*/*z* 291.1 ($M-H^+$). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N; 9.58. Found: C, 57.60; H, 5.54; N; 9.50.
Methyl 4-(4-hydroxy-3-methoxy-5-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4p**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.42 (s, 1H, OH), 9.30 (s, 1H, NH), 7.81 (s, 1H, NH), 7.23 (s, 1H, ArH), 7.17 (s, 1H, ArH), 5.17 (s, 1H, CH), 3.86 (s, 3H, OCH_3), 3.06 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.7, 151.9, 149.4, 141.9, 136.6, 135.1, 114.6, 112.4, 98.0, 56.4, 53.0, 50.9, 17.9. IR (KBr): 3353, 3213, 3089, 2951, 2844, 1681, 1649, 1548 cm^{-1}. MS (ESI): *m*/*z* 337.5 (M^-). Anal. Calcd for $C_{14}H_{15}N_3O_7$: C, 49.86; H, 4.48; N; 12.46. Found: C, 49.90; H, 4.36; N; 12.51.
Methyl 4-(3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4r**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 1H, NH), 7.76 (s, 1H, NH), 7.26–7.22 (m, 1H, ArH), 6.83–6.78 (m, 3H, ArH), 5.13 (s, 1H, CH), 3.73 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.8, 159.3, 152.2, 148.8, 146.1, 129.6, 118.1, 112.4, 112.1, 98.8, 54.9, 53.6, 50.8, 17.8. IR (KBr): 3218, 3098, 3000, 2951, 2836, 1700, 1642, 1608, 1587 cm^{-1}. MS (ESI): *m*/*z* 275.3 ($M-H^+$). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N; 10.14. Found: C, 60.71; H, 5.82; N; 10.23.
Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4v**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H, NH), 9.54 (s, 1H, NH), 7.01 (d, 2H, $J = 8.4$ Hz, ArH), 6.66 (d, 2H, $J = 8.4$ Hz, ArH), 5.05 (s, 1H, CH), 3.99 (q, 2H, $J = 6.8$ Hz, OCH_2CH_3), 2.86 (s, 6H, $N(CH_3)_2$), 2.27 (s, 3H, CH_3), 1.12 (t, 3H, $J = 6.8$ Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.8, 165.3, 149.9, 144.3, 131.2, 127.1, 112.2, 101.2, 59.5, 53.5, 40.1, 17.1, 14.1. IR (KBr): 3327, 3169, 2986, 1671, 1650, 1616, 1580, 1524, 1466, 1364, 1322, 1188, 1099 cm^{-1}. MS (ESI): *m*/*z* 320.1 ($M+H^+$). Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.21; H, 6.63; N; 13.16. Found: C, 60.28; H, 6.60; N; 13.18.
Ethyl 6-methyl-2-thioxo-4-p-tolyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4x**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (s, 1H, NH), 9.61 (s, 1H, NH), 7.12 (d, 2H, $J = 8.0$ Hz, ArH), 6.90 (d, 2H, $J = 8.0$ Hz, ArH), 5.12 (s, 1H, CH), 4.00 (q, 2H, $J = 6.8$ Hz, OCH_2CH_3), 3.72 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 1.11 (t, 3H, $J = 6.8$ Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.0, 165.1, 158.7, 144.7, 135.7, 127.6, 113.9, 100.9, 59.5, 55.0, 53.4, 17.1, 14.0. IR (KBr): 3313, 3171, 3106, 2985, 1667, 1610, 1575, 1509, 1461, 1371 cm^{-1}.