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# One-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using chloroacetic acid as catalyst

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**Abstract**—A simple and effective synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives from aldehydes, 1,3-dicarbonyl compounds and urea or thiourea using chloroacetic acid as catalyst under solvent-free conditions is described. Compared with the classical Biginelli reaction conditions, this new method has the advantage of good to excellent yields and short reaction time.

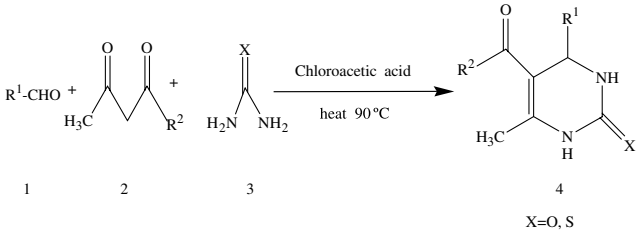

Dihydropyrimidinone derivatives have attracted considerable interest in recent years because of therapeutic and pharmacological properties nowadays. For example, they can serve as the integral backbones of several calcium channel blockers,[1] antihypertensive agents[2] and α-1a-antagonists.[3] In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also show interesting biological activities.[4]

The classical Biginelli reaction of an aldehyde, 1,3-dicarbonyl and urea or thiourea requires strongly acidic conditions with relatively low yields.[5] In order to improve the efficiency of Biginelli reaction, a lot of catalysts, such as zirconium(IV) chloride,[6] indium(III) bromide,[7] ytterbium(III) resin,[8] ionic liquids ($BMImPF_6$ and $BMImBF_4$),[9] ceric ammonium nitrate (CAN),[10] manganese acetate,[11] lanthanide triflate,[12] indium(III) chloride,[13] lanthanum chloride,[14] copper(II) triflate,[15] *p*-TsOH,[16] $KHSO_4$,[17] silica sulfuric acid,[18] $H_3PW_{12}O_{40}$,[19] $H_3PMo_{12}O_{40}$[20] and so on, have been developed. Some of them are really fascinating from the synthetic chemist's points, however, some drawbacks still remain. For example, some catalysts are expensive, complex or unavailable and organic solvents are always used. Furthermore, many heavy metallic salts were used which resulted in the pollution to environment to some extent.

In connection with our previous work on the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones using convenient and inexpensive acid as a catalyst,[21] we wish to report a simple but effective procedure for Biginelli's three-component condensation producing high yields of 3, 4-dihydropyrimidin- 2(1*H*)-ones by employing chloroacetic acid as a sort of efficient catalyst (Scheme 1).

First, we groped for the optimized reaction conditions. To optimize the reaction conditions, the reaction of benzaldehyde, ethyl acetoacetate and urea was selected as model to investigate the effects of the catalyst at different reaction temperatures (rt 70, 80 and 90 °C) and the different dosages of catalyst (5, 10 and 20 mol%) on the yield. The best result in 92% yield was obtained by carrying out the reaction with 1:1.1:1.5 mol ratios of aldehyde, 1,3-dicarbonyl, urea or thiourea at 90 °C and the dosage of 10 mol% catalyst for 3 h under solvent-free conditions.[22]

Using the above optimized reaction conditions, then the reactions of various aldehydes, 1,3-dicarbonyl compounds and urea or thiourea were investigated. The




**Scheme 1.**

*Keywords*: Chloroacetic acid; Biginelli reaction; Dihydropyrimidinones; One-pot; Synthesis; Solvent-free.
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**Table 1.** Synthesis of dihydropyrimidin-2(*H*)-ones and thiones catalyzed by chloroacetic acid under solvent-free conditions at 90 °C

| Compound | $R^1$ | $R^2$ | X | Time (h) | Yield[a] (%) | Mp (°C) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Found | Reported |
| **4a** | $C_6H_5$ | OEt | O | 3 | 92 | 198–200 | 200–202[24] |
| **4b** | 4-(Cl)-$C_6H_4$ | OEt | O | 3 | 98 | 211–213 | 209–211[25] |
| **4c** | 4-($CH_3O$)-$C_6H_4$ | OEt | O | 3 | 95 | 203–205 | 201–202[26] |
| **4d** | 4-($CH_3$)-$C_6H_4$ | OEt | O | 3 | 86 | 213–216 | 214–215[26] |
| **4e** | 2,4-$(Cl)_2$-$C_6H_3$ | OEt | O | 3 | 89 | 246–248 | 248–250[27] |
| **4f** | $C_3H_7$ | OEt | O | 5 | 75 | 180–182 | 179–180[28] |
| **4g** | $(CH_3)_2$ CH | OEt | O | 5 | 47 | 196–197 | 195–197[28] |
| **4h** | $C_6H_5$ | OMe | O | 3 | 92 | 210–213 | 209–212[29] |
| **4i** | 4-(Cl)-$C_6H_4$ | OMe | O | 3 | 97 | 207–208 | 206–208[19] |
| **4j** | 4-($CH_3O$)-$C_6H_4$ | OMe | O | 3 | 97 | 193–196 | 193–196[30] |
| **4k** | 4-($CH_3$)-$C_6H_4$ | OMe | O | 3 | 93 | 210–213 | 204–206[7] |
| **4l** | 2,4-$(Cl)_2$-$C_6H_3$ | OMe | O | 3 | 93 | 252–253 | 254–255[12] |
| **4m** | $(CH_3)_2$ CH | OMe | O | 5 | 50 | 217–218 | 216–218[28] |
| **4n** | $C_6H_5$ | Me | O | 3 | 88 | 230 | 233–236[12] |
| **4o** | 4-(Cl)-$C_6H_4$ | Me | O | 3 | 97 | 230–232 | 233–235[29] |
| **4p** | 4-($CH_3O$)-$C_6H_4$ | Me | O | 3 | 94 | 176–178 | 177–179[30] |
| **4q** | $C_6H_5$ | OEt | S | 5 | 84 | 202–204 | 205–206[31] |
| **4r** | 4-($CH_3O$)-$C_6H_4$ | OEt | S | 5 | 86 | 137–139 | 136–138[31] |
| **4s** | 4-(Cl)-$C_6H_4$ | OEt | S | 5 | 87 | 184–185 | 180–182[31] |
| **4t** | 4-(OH)-$C_6H_4$ | OEt | S | 5 | 79 | 193–195 | 193–194[32] |
| **4u** | $C_6H_5$ | OMe | S | 5 | 83 | 221–222 | 222[33] |

[a] Isolated yields.

results are shown in Table 1 and all the products were characterized by mp, IR and $^1$H NMR spectra.[23]

In all cases studied, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in satisfactory yields. Most important, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted efficiently and gave good to excellent yields. Even for aliphatic aldehydes which usually show extremely poor yields in the Biginelli reaction, 75%, 47% and 50% yields of the corresponding dihydropyrimidin-2(1*H*)-ones **4f**, **4g** and **4m** could be obtained with a slightly longer reaction time. In addition, acetylacetone and thiourea were also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones.

Meanwhile we also performed several experiments in the absence of chloroacetic acid under the same reaction conditions. For example, when the reaction was executed in the presence of chloroacetic acid the yields of **4a**, **4b**, **4c**, **4f**, **4i**, **4j** and **4k** in Table 1 were 92%, 98%, 95%, 75%, 97%, 97% and 93%, respectively, however, the corresponding yields were 71%, 59%, 45%, 60%, 73%, 46% and 58%, respectively, in the absence of chloroacetic acid. Furthermore, in order to show the excellent catalytic activity of the catalyst, we carried out the synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (entry **4a** in Table 1) catalyzed by other several Brønsted acid catalysts under the same reaction conditions (Table 2).

Table 2 shows that the yield of the desired product in the presence of chloroacetic acid is higher than that in the presence of other Brønsted acid catalysts. From the results mentioned above, chloroacetic acid is an excellent catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones through Biginelli reaction.

**Table 2.** Comparison the results of the 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one using different Brønsted acid catalysts

| Catalysts (10 mol%) | Yield (%) |
|---|---|
| Chloroacetic acid | 92 |
| Acetic acid | 80 |
| Phosphotungstic acid | 87 |
| Phosphomolybdic acid | 80 |
| Potassium acid sulfate | 78 |
| Trifluoroacetic acid | 72 |
| Bromoacetic acid | 80 |
| Trichloroacetic acid | 71 |
| *p*-Toluenesulfonic acid | 88 |

In conclusion, an efficient procedure for the synthesis of dihydropyrimidinones by using chloroacetic acid as an inexpensive and easily available catalyst was developed. This procedure is much simpler and faster than the protocols published to date. It is also consistent with a green chemistry approach since no solvent is needed.

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22. A mixture of aldehyde (25 mmol), 1,3-dicarbonyl compounds (27.5 mmol), urea or thiourea (37.5 mmol) and chloroacetic acid (2.5 mmol) under solvent-free conditions was heated to 90 °C for the required time in a 100 mL conical flask in water bath. After cooling, the reaction mixture was poured into crushed ice and stirred for 5–10 min. The solid was filtered under suction, washed with ice-cold water and then recrystallized from ethanol to afford pure product.
23. Some selected data are as follows:
*5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4b**)*. IR (KBr): 3243, 1724, 1647, 840 $cm^{-1}$, $^1H$ NMR (DMSO-$d_6$): $\delta$ = 9.26 (s, 1H, NH), 7.76 (s, 1H, NH), 7.39-7.25 (m, 4H, $C_6H_4$), 5.14 (s, 1H, CH), 3.96 (q, $J$ = 7.0 Hz, 2H, $OCH_2CH_3$), 2.24 (s, 3H, $CH_3$), 1.09 (t, $J$ = 7.0 Hz, 3H, $OCH_2CH_3$).
*5-Ethoxycarbonyl-6-methyl-4-(2,4-dichlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4e**)*. IR (KBr): 3360, 1698, 1645, 875, 816 $cm^{-1}$, $^1H$ NMR (DMSO-$d_6$): $\delta$ = 9.35(s, 1H, NH), 7.79(s, 1H, NH), 7.52(s, 1H, arom CH), 7.42 (d, $J$ = 8.4 Hz, 1H, arom CH), 7.36(d, $J$ = 8.4 Hz, 1H, arom CH), 5.63 (s, 1H, CH), 3.90 (q, $J$ = 7.1 Hz, 2H, $OCH_2CH_3$), 2.28 (s, 3H, $CH_3$), 1.02 (t, $J$ = 7.1 Hz, 3H, $OCH_2CH_3$).
*5-Ethoxycarbonyl-6-methyl-4-propyl-3,4-dihydropyrimidin-2(1H)-one (**4f**)*. IR (KBr): 3251, 3120, 2958, 2935, 2874, 1720, 1647 $cm^{-1}$, $^1H$ NMR (DMSO-$d_6$): $\delta$ = 8.93 (s, 1H, NH), 7.32 (s, 1H, NH), 4.10–4.04 (q, $J$ = 4.7 Hz, 3H, H-4 and $OCH_2CH_3$), 2.15 (s, 3H, $CH_3$), 1.26–1.40 (m, 4H, $CH_2CH_2CH_3$), 1.21–1.16 (t, $J$ = 4.7 Hz 3 H, $OCH_2CH_3$), 0.87-0.83 (t, $J$ = 6.9 Hz, 3H, $CH_2CH_2CH_3$).
*5-Methoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4i**)*. IR (KBr): 3366, 1716, 1636 $cm^{-1}$, $^1H$ NMR (DMSO-$d_6$): $\delta$ = 9.27 (s, 1H, NH), 7.74 (s, 1H, NH), 7.41–7.22 (m, 4H, $C_6H_4$), 5.14 (s, 1H, CH), 3.53 (s, 3H, $CH_3OCO$), 2.24 (s, 3H, $CH_3$).
*5-Methoxycarbonyl-6-methyl-4-(2,4-dichlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4l**)*. IR (KBr): 3362, 1697, 1647, 845, 820 $cm^{-1}$, $^1H$ NMR (DMSO-$d_6$): $\delta$ = 9.33 (s, 1 H, NH), 7.78 ( s, 1H, NH), 7.57 (s, 1H, arom CH), 7.38 (d, $J$ = 8.4 Hz, 1H, arom CH), 7.30 (d, $J$ = 8.4 Hz, 1H, arom CH), 5.60 (s, 1H, CH), 3.48 (s, 3H, $CH_3OCO$), 2.57 (s, 3H, $CH_3$).
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