

Synthesis and Acylation of 4-Chloroalkyl-3,4-dihydropyrimidin-2(1H)-ones

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4-Chloroalkyl-3,4-dihydropyrimidin-2(1H)-ones are useful multifunctional 3,4-dihydropyrimidine building blocks with low molecular weight and sufficient solubility, which may be modified selectively by substituents in different positions. Here we propose a simple one-pot protocol for the synthesis of these compounds, which is based on the use of common reagents *viz.* urea, chloroaliphatic aldehydes and 3-ketoesters. Acylation of 4-chloroalkyl-3,4-dihydropyrimidin-2(1H)-ones by carboxylic acid anhydrides leads to 3-acyl derivatives.

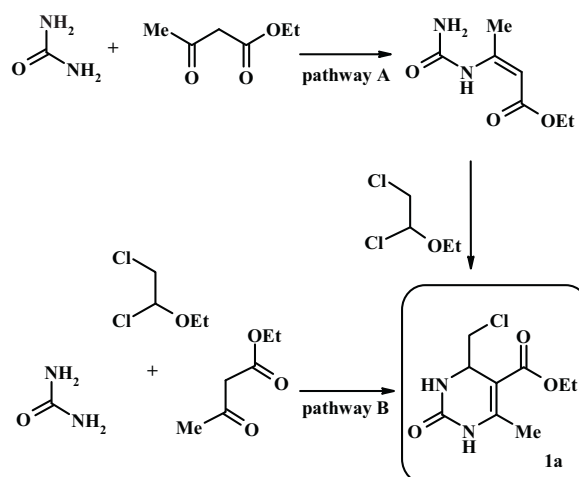
Key words: 3,4-Dihydropyrimidin-2(1H)-ones, Biginelli Reaction, Chloroaliphatic Aldehydes, One-pot Synthesis, Acylation

Introduction

Biginelli compounds (namely, the derivatives of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones) are readily available heterocycles [1–3]. This fact has caused a tremendous number of publications in this area [3]. In contrast, promising multifunctional compounds, such as 4-chloroalkyl derivatives of 3,4-dihydropyrimidin-2(1H)-ones, are rather poorly known [4–8].

For example, the most usual pathways of 4-chloromethyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one synthesis consist of two-step [4, 5] (pathway A, Scheme 1) or one-step protocols (pathway B, Scheme 1) [6], but necessarily involve the use of 1,2-dichloroethyl ethyl ether. So, the use of other chloroaliphatic aldehydes or their derivatives is limited and still remains unexplored.

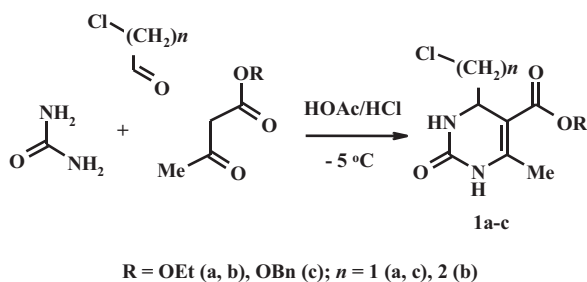
Here we report a simple and cheap protocol for the one-pot synthesis of 5-alkoxycarbonyl-4-chloroalkyl-6-methyl-3,4-dihydropyrimidin-2(1H)-ones starting from very common reagents, namely aliphatic aldehydes, urea and acetoacetic esters, and discuss their acylation.



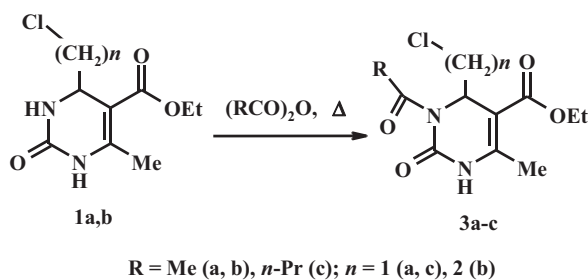
Scheme 1. Known pathways for the synthesis of 4-chloromethyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1a**).

Results and Discussion

The most common reagents for the synthesis of Biginelli compounds are solvent/catalyst systems such as ethanol/HCl [9], glacial HOAc [9], DMF/TMSCl



Scheme 2. Procedure for the synthesis of target 4-chloroalkyl-3,4-dihydropyrimidin-2(1*H*)-ones **1a–c**.



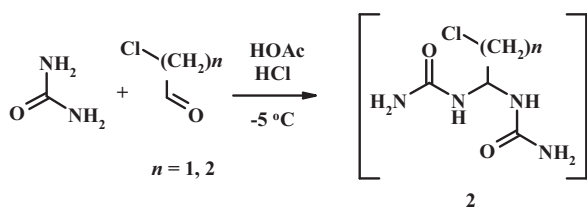
Scheme 4. Acylation of 4-chloroalkyl-3,4-dihydropyrimidin-2(1*H*)-ones **1a, b**.

[10, 11] or pure DMF [12]. Depending on the starting compounds, different systems of solvent/catalyst [13] and ratios of reagents [9, 14, 15] may be used, but heating is needed in all cases.

We have now found, that the optimal conditions for the synthesis of compounds **1a–c** from urea, chloroaliphatic aldehydes and alkyl acetoacetates include glacial HOAc/dry HCl as solvent/catalyst system and cooling of the reaction mixture to about $-5\text{ }^{\circ}\text{C}$ with prolonged stirring (see Experimental Section, Scheme 2).

When alcohol/HCl or DMF were used, the products **1** were not obtained, and only dark mixtures of polymers were formed. The same was noted upon heating; no experiments with heating were successful.

One of the important details of the improved protocol is the addition of the reagents in turns. First the aldehyde and urea should be dissolved, then the ketoester should be added, and the solution should then be saturated with dry HCl. During the saturation with HCl a precipitate is formed, which completely dissolves after further gas bubbling. Taking into consideration the mechanism of the acid-catalyzed Biginelli reaction [16], an alkylidene-*bis*-urea **2** may be proposed for the initial precipitate (Scheme 3).



Scheme 3. Possible scheme of the initial precipitate formation.

The best ratio of reagents are equimolar amounts of urea and ketoester with 1.5 equivalents of aldehyde. Noteworthy, compounds **1** turned out to be much more soluble in alcohols and ethyl acetate than their 4-aryl analogs.

Acylation of compounds **1a, b** with carboxylic acid anhydrides occurred smoothly and led to the 3-acyl derivatives **3a–c**, the spectroscopic and physical data of which agreed well with literature data [17, 18] (Scheme 4).

An attempt to obtain the 1-methyl derivative of compound **1a** under the conditions of phase-transfer catalysis (MeI, saturated KOH-H₂O, MeCN [19]) was unsuccessful; this may be caused by auto-alkylation of compound **1a** and/or processes of its recyclization [4–8].

Conclusion

We worked out a simple protocol for the synthesis of 5-alkoxycarbonyl-4-chloroalkyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-ones starting from the common reagents aldehydes, urea and alkyl acetoacetates. The moderate yields of the target products are completely compensated by the availability and low cost of the starting compounds.

Experimental Section

Chloroacetaldehyde, urea, and alkyl acetoacetates were commercially available. 3-Chloropropanal was obtained as described in ref. [20]. Melting points were determined using a Kofler hot-stage apparatus. ¹H NMR spectra were recorded in [D₆]DMSO at 200 MHz using a Varian Mercury VX-200 spectrometer with Si(CH₃)₄ as internal standard. Chemical shifts are reported in ppm (δ scale), coupling constants are given in Hz. Mass spectra (EI, 70 eV) were obtained using a Varian 1200L instrument using a direct probe expo-

sure method. IR spectra were recorded on KBr pellets using a Specord IR-75 spectrometer. Elemental analyses (C, H, N) were performed by standard combustion procedure, their results were found to be in good agreement ($\pm 0.3\%$) with the calculated values.

5-Alkoxy carbonyl-4-chloroalkyl-6-methyl-3,4-dihydropyrimidin-2(1H)-ones 1a–c. General procedure

To a solution of 2.00 g (0.033 mol) of urea in 15 mL of glacial HOAc 0.05 mol of the appropriate chloroaliphatic aldehyde (50% water solution in the case of 2-chloroacetaldehyde) was added. Then 0.033 mol of an appropriate alkyl acetoacetate was added, and the mixture was cooled to $-10\text{ }^\circ\text{C}$ (ice/NaCl bath). The mixture was saturated with dry HCl at $-5\text{ }^\circ\text{C}$ (heating takes place) with vigorous stirring. The process of saturation took 4–5 h, and the mixture turned pale yellow. It was allowed to react for about 12–20 h, and under cooling the pH of the mixture was adjusted to neutral by addition of conc. aqueous Na_2CO_3 solution (about 250 mL). The formed precipitate was filtered off, washed with water and 70% aqueous methanol to remove unreacted ketoester. Work-up of the mother liquor did not lead to the isolation of additional portions of the target compounds. Compounds **1a–c** can be crystallized from acetone or an EtOAc-hexane (1 : 1) mixture.

4-Chloromethyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (1a)

Yield 32%. M. p. $176\text{--}177\text{ }^\circ\text{C}$ (lit. [4]: m. p. $176.5\text{--}177\text{ }^\circ\text{C}$). – IR (KBr, cm^{-1}): $\nu = 1672$ (C=O), 1735 (C=O), 2929, 3123, 3216 (NH). – ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.19$ (t, $J = 7.0$, 3 H, CH_2CH_3), 2.17 (s, 3 H, CH_3), 3.45–3.64 (m, 2 H, CH_2Cl), 4.07 (q, $J = 7.0$, 2 H, CH_2CH_3), 4.30–4.45 (m, 1 H, C(4)H), 7.43 (br. s, 1 H, N(3)H), 9.18 (br. s, 1 H, N(1)H). – MS (EI, 70 eV): $m/z(\%) = 183$ (100) $[\text{M}-\text{CH}_2\text{Cl}]^+$, 155 (35), 137 (40). – Anal. for $\text{C}_9\text{H}_{13}\text{ClN}_2\text{O}_3$: calcd. C 46.46, H 5.63, N 12.04; found C 46.70, H 5.87, N 11.85.

4-(2-Chloroethyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (1b)

Yield 20%. M. p. $187\text{--}188\text{ }^\circ\text{C}$. – IR (KBr, cm^{-1}): $\nu = 1642$ (C=O), 1708 (C=O), 3116, 3229 (NH). – ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.17$ (t, $J = 7.0$, 3 H, CH_2CH_3), 1.65–1.95 (m, 2 H, $\text{CH}_2\text{CH}_2\text{Cl}$), 2.17 (s, 3 H, CH_3), 3.61 (t, $J = 6.0$, 2 H, CH_2Cl), 3.90–4.15 (m, 2 H, CH_2CH_3), 4.13–4.30 (m, 1 H, C(4)H), 7.52 (br. s, 1 H, N(3)H), 9.09 (br. s, 1 H, N(1)H). – MS (EI, 70 eV): $m/z(\%) = 201$ (10) $[\text{M}-\text{OEt}]^+$, 183 (100), 155 (70), 137 (60). – Anal. for $\text{C}_{10}\text{H}_{15}\text{ClN}_2\text{O}_3$: calcd. C 48.69, H 6.13, N 11.36; found C 46.51, H 5.98, N 11.08.

5-Benzoyloxycarbonyl-4-chloromethyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (1c)

Yield 6%. M. p. $210\text{--}211\text{ }^\circ\text{C}$. – IR (KBr, cm^{-1}): $\nu = 1655$ (C=O), 1702 (C=O), 3116, 3376 (NH). – ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 2.20$ (s, 3 H, CH_3), 3.43–3.60 (m, 2 H, CH_2Cl), 4.35–4.45 (m, 1 H, C(4)H), 5.10 (s, 2 H, OCH_2), 7.10–7.60 (m, 6 H, Ph + N(3)H), 9.20 (br. s, 1 H, N(1)H). – MS (EI, 70 eV): $m/z(\%) = 245$ (15) $[\text{M}-\text{Ph}]^+$, 110 (10), 91 (100). – Anal. for $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_3$: calcd. C 57.05, H 5.13, N 9.50; found C 56.97, H 4.90, N 9.62.

3-Acyl-4-chloroalkyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-ones 3a–c. General procedure

A mixture of of compound **1** (2.6 mmol) with the appropriate carboxylic acid anhydride (40 mmol) was stirred at $150\text{ }^\circ\text{C}$ for 3 h. The mixture was cooled, poured into water and allowed to mix for 6–12 h. The precipitate of compound **3** was filtered off and washed with water. Compounds **3a–c** can be recrystallized from EtOH.

3-Acetyl-4-chloromethyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (3a)

Yield 75%. M. p. $152\text{--}153\text{ }^\circ\text{C}$. – IR (KBr, cm^{-1}): $\nu = 1662$ (C=O), 1702 (C=O), 2978, 3163, 3269 (NH). – ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.20$ (t, $J = 7.0$, 3 H, CH_2CH_3), 2.23 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 3.55–3.75 (m, 2 H, CH_2Cl), 4.12 (q, $J = 7.0$, 2 H, CH_2CH_3), 5.62 (t, $J = 4.7$, 2 H, C(4)H), 10.11 (br. s, 1 H, N(1)H). – MS (EI, 70 eV): $m/z(\%) = 229$ (10) $[\text{M}-\text{OEt}]^+$, 225 (15), 183 (100), 155 (40), 137 (30). – Anal. for $\text{C}_{11}\text{H}_{15}\text{ClN}_2\text{O}_4$: calcd. C 48.10, H 5.50, N 10.20; found C 47.95, H 5.43, N 9.98.

3-Acetyl-4-(2-chloroethyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (3b)

Yield 59%. M. p. $176\text{--}177\text{ }^\circ\text{C}$. – IR (KBr, cm^{-1}): $\nu = 1642$ (C=O), 1702 (C=O), 3183, 3263 (NH). – ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.20$ (t, $J = 7.0$, 3 H, CH_2CH_3), 1.78–2.00 (m, 2 H, $\text{CH}_2\text{CH}_2\text{Cl}$), 2.21 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 3.45 (t, $J = 6.8$, 2 H, CH_2Cl), 4.00–4.20 (m, 2 H, CH_2CH_3), 3.55–3.75 (m, 2 H, CH_2Cl), 5.50 (t, $J = 6.6$, 1 H, C(4)H), 10.10 (br. s, 1 H, N(1)H). – MS (EI, 70 eV): $m/z(\%) = 225$ (15) $[\text{M}-\text{CH}_2\text{CH}_2\text{Cl}]^+$, 183 (100), 137 (45). – Anal. for $\text{C}_{12}\text{H}_{17}\text{ClN}_2\text{O}_4$: calcd. C 49.92, H 5.93, N 9.70; found C 50.08, H 5.90, N 9.82.

3-Butyryl-4-chloromethyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (3c)

Yield 52%. M. p. $112\text{--}113\text{ }^\circ\text{C}$. – IR (KBr, cm^{-1}): $\nu = 1668$ (C=O), 1705 (C=O), 3103, 3149 (NH). – ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 0.86$ (t, $J = 7.0$, 3 H,

(CH₂)₂CH₃), 1.21 (t, *J* = 7.0, 3 H, CH₂CH₃), 1.40–1.70 (m, 2 H, CH₂CH₂CH₃), 2.23 (s, 3 H, CH₃), 2.58–2.78 (m, 1 H, CH₂C₂C₃), 2.83–3.03 (m, 1 H, CH₂C₂C₃), 3.55–3.75 (m, 2 H, CH₂Cl), 4.12 (q, *J* = 7.0, 2 H, CH₂CH₃), 5.62 (t, *J* = 4.4, 1 H, C(4)H), 10.12 (br. s, 1 H, N(1)H). – MS (EI, 70 eV): *m/z*(%) = 257 (10) [M–EtO]⁺, 253 (15) [M–CH₂Cl]⁺, 183 (100). – Anal. for C₁₃H₁₉ClN₂O₄: calcd. C 51.57, H 6.33, N 9.25; found C 51.58, H 6.30, N 9.00.

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